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Review article

Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update (in collaboration with the World Health Organization, GA^{2}LEN* and AllerGen**)

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1. Introduction

Allergic rhinitis is a symptomatic disorder of the nose induced after allergen exposure by an immunoglobulin E (IgE)-mediated inflammation of the membranes lining the nose (1). It was defined in 1929 (2): 'The three cardinal symptoms in nasal reactions occurring in allergy are sneezing, nasal obstruction and mucous discharge'.

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Patients from all countries, all ethnic groups and of all ages suffer from allergic rhinitis. It affects social life, sleep, school and work. The economic impact of allergic rhinitis is often underestimated because the disease does not induce elevated direct costs. However, the indirect costs are substantial (1). Both allergic rhinitis and asthma are systemic inflammatory conditions and are often co-morbidities.

Although asthma and other forms of allergic disease have been described in antiquity, 'hay fever' is surprisingly modern. Very rare descriptions can be traced back to

Abbreviations: AAAAI, American Academy of Allergy, Asthma and Immunology; ABPA, allergic bronchopulmonary aspergillosis; ACAAI, American College of Allergy, Asthma and Immunology; AGREE, Appraisal of Guideline Research & Evaluation; AIA, aspirin-induced asthma; AIANE, European Network on Aspirin-Induced Asthma; ANAES, Agence Nationale de l'Accréditation et d'Evaluation en Santé; AOM, acute otitis media; AQLQ questionnaire, asthma quality of life questionnaire; ARIA, Allergic Rhinitis and its Impact on Asthma; ATS, American Thoracic Society; BCG, Bacille de Calmette et Guérin; Bet v 1, *Betula verucosa* antigen 1 (major birch pollen allergen); CAM, complementary and alternative medicine; CD, Cluster of Differentiation; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CNS, central nervous system; CO, carbon monoxide; CO_2, carbon dioxide; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CRD, chronic respiratory diseases; CRS, chronic rhinosinusitis; CT scan, computerized tomography scan; CXCR, CXC chemokine receptor; CysLT, cysteinyl leukotrienes; DALY, disability-adjusted life years; Der f, *Dermatophagoides farinae;* Der p 1, *Dermatophagoides pteronyssinus* antigen 1 (major HDM allergen); DPT, Dipheteria-Tetanus-Pertussis; EAACI, European Academy of Allergology and Clinical Immunology; EBM, evidence-based medicine; ECRHS, European Community Respiratory Health Survey; ECM, extracellular matrix; ECP, eosinophil cationic protein; EFA, European Federation of Allergy & Airway diseases patients association; EIA, exercise-induced asthma; EIB, exercise-induced bronchoconstriction; Equ c, *Equus caballus* (horse); ETS, environmental tobacco smoke; Eur m, *Euroglyphus maynei;* EVH, Eucapnic Voluntary Hyperventilation; FceRI, high affinity receptor for IgE; FceRII, low affinity receptor for IgE (CD23); Fel d 1, *Felix domesticus* allergen 1 (major cat allergen); FEV_1, forced expiratory volume in 1 s; FLAP, 5-lipoxygenase (LO) activating protein; FVC, forced vital capacity; GARD, WHO Global Alliance against chronic Respiratory Diseases; GER, gastro-oesophageal reflux; GM-CSF, granulocyte, monocyte colony-stimulating factor; GR, glucocorticosteroid receptor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GRE, glucocorticosteroid receptor responsive element; HDM, house dust mite; HEPA, High Efficiency Particulate Air Filter; HETE, hydroxyeicosatetraenoic acid; HPA axis, hypothalamic-pituitary-adrenal axis; HPETE, hydroperoxyeicosatetraenoic acid; HRQOL, health-related quality of life; IAR, intermittent allergic rhinitis; IPAG, International Primary Care Airways Group; IPCRG, International Primary Care Respiratory Group; ISAAC, International Study on Asthma and Allergy in Childhood; IU, International Unit; IUIS, International Union of Immunological Societies; Lep d, *Lepidoglyphus destructor;* LTC_4, leukotriene C_4; LTD_4, leukotriene D_4; LRT, lower respiratory tract; mAb, monoclonal antibody; MAS, German Multicenter Allergy Study; MMR, Measle-Mumps-Rubella; MMPs, Matrix Metallo Proteinases; mRNA, messenger ribonucleic acid; Mus m, *Mus musculus;* NANC, nonadrenergic, noncholinergic; NAR, nasal airway resistance; NARES, nonallergic rhinitis with eosinophilia syndrome; NHANES II, second National Health and Nutrition Examination Survey (USA); NIH, National Institutes of Health; NO, nitric oxide; NO_2, nitrogen dioxide; NP, nasal polyp; NSAID, nonsteroidal anti-inflammatory drug; OAD, occupational asthma; OME, otitis media with effusion; OR, odds ratio; Ory c, *Oryctolagus cuniculus;* OSAS, obstructive sleep apnoea syndrome; OTC, over-the-counter; PADQLQ, Paediatric Allergic Disease Quality of Life Questionnaire; PCR, polymerase chain reaction; PDGF, platelet-derived growth factor; PedsQL , paediatric quality of life inventory; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; PAR, persistent allergic rhinitis; PG, prostaglandin; Phl p, *Phleum pratense;* PIAMA, Prevention and Incidence of Asthma in Mite Allergy; PM10, particulate matter < 10 μm; PNIF, peak nasal inspiratory flow; PRIST, paper radioimmunosorbent test; PRN, as needed; QALY, quality-adjusted life years; QOL, quality of life; QTc, QT interval; Rat n, *Rattus norvegicus;* RAST, radioallergosorbent test; RCT, randomized-controlled trial; RQLQ, rhinoconjunctivitis quality of life questionnaire; RSV, respiratory syncytial virus; SAPALDIA, Swiss Study on Air Pollution and Lung Diseases in Adults; SCARPOL, Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen; SCIT, subcutaneous immunotherapy; SF36, medical outcome short form 36 questions; SIGN, Scottish intercollegiate network; SIT, specific immunotherapy; SLIT, sublingual immunotherapy; SO_2, sulphur dioxide; Th, T helper lymphocyte; UDA, Usual Daily Activity; URT, upper respiratory tract; VAS, visual analogue scale; VCAM-1, vascular cellular adhesion molecule 1; VEGF, Vascular Endothelial Growth Factor; VOC, volatile organic compound; WHO, World Health Organization; WRAD, work-related occupational disease.

Islamic texts of the 9th century and European texts of the 16th century. It was only in the early 19th century that the disease was carefully described, and at that time it was regarded as most unusual (3). In the 19th century, the disease followed the industrialization of westernized countries (4). By the end of the 19th century it had become commonplace in both Europe and North America. However, the prevalence of allergic rhinitis was still low and has considerably increased during the past 50 years. In some countries, over 50% of adolescents are reporting symptoms of allergic rhinitis (5). Using a conservative estimate, allergic rhinitis occurs in over 500 million people around the world. The prevalence of allergic rhinitis is increasing in most countries of the world, and particularly in areas with low or medium levels of prevalence. However, it may be plateauing or even decreasing in the highest prevalence areas. Rhinitis and allergic diseases are now taken seriously and the European Union (6) or countries such as Canada have specific programs to better understand, manage and prevent allergic diseases.

Risk factors for allergic rhinitis are well identified. In the middle of the 19th century, the cause of hay fever was ascribed to pollens (7, 8). Indoor and outdoor allergens as well as occupational agents cause rhinitis and other allergic diseases. The role of indoor and outdoor pollution is probably very important, but has yet to be fully understood both for the occurrence of the disease and its manifestations.

The diagnosis of allergic rhinitis is often easy, but in some cases it may cause problems and many patients are still underdiagnosed, often because they do not perceive the symptoms of rhinitis as a disease impairing their social life, school and work.

The management of allergic rhinitis is well established and many guidelines have been issued although the first ones were not evidence based (9–11).

1.1. The ARIA workshop

In 1999, during the Allergic Rhinitis and its Impact on Asthma (ARIA) World Health Organization (WHO) workshop, the suggestions were made by a panel of experts and based on evidence using an extensive review of the literature available up to December 1999 (1). The statements of evidence for the development of these guidelines followed WHO rules and were based on those of Shekelle et al. (12).

The second important achievement of ARIA was to propose a new classification for allergic rhinitis which was subdivided into 'intermittent' (IAR) or 'persistent' (PER) disease (1).

Moreover, it is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhoea and nasal obstruction. It is associated with impairments in how patients function in day-to-day life. The severity of allergic rhinitis was therefore classified as 'mild' or 'moderate/severe' depending on symptoms but also on quality of life (QOL; 1).

Another important aspect of the ARIA guidelines was to consider co-morbidities of allergic rhinitis. Eye involvement in allergic rhinitis has been described for a long time (13). The nasal airways and their closely-associated paranasal sinuses are an integral part of the respiratory tract (1, 14–16). In the second century, *Claudius Galenus*, one of the fathers of modern respiratory physiology, defined the nose as a 'respiratory instrument' in his work *De usu partium* [on the usefulness of the (body) parts (17)]. The co-morbidities between the upper and lower airways were described with the clinical description of allergic rhinitis (3, 8). The nasal and bronchial mucosa present similarities, and one of the most important concepts regarding nose–lung interactions is the functional complementarity (14). Interactions between the lower and the upper airways are well known and have been extensively studied since 1990. Over 80% of asthmatics have rhinitis and 10–40% of patients with rhinitis have asthma (1). Most patients with asthma have rhinitis (18) suggesting the concept of 'one airway one disease' although there are differences between rhinitis and asthma (19, 20).

The ARIA document was intended to be a state-of-the-art for the specialist as well as for the general practitioner and other healthcare professionals:

- to update their knowledge of allergic rhinitis;
- to highlight the impact of allergic rhinitis on asthma;
- to provide an evidence-based documented revision on diagnostic methods;
- to provide an evidence-based revision on treatments and
- to propose a stepwise approach to management.

The ARIA document was not intended to be a standard-of-care document for individual countries. It was provided as a basis for doctors, healthcare professionals and organizations involved in the treatment of allergic rhinitis and asthma in various countries to facilitate the development of relevant local standard-of-care documents for patients.

The ARIA workshop held at the WHO headquarters proposed the recommendations shown in Table 1.

1.2. Need for an ARIA update

An update of the ARIA guidelines was needed because:

- a large number of papers have been published over the past 7 years extending our knowledge on the epidemiology, diagnosis, management and co-morbidities of allergic rhinitis. Other guidelines have been produced since 1999 (21), but these did not review the ongoing literature extensively using an evidence-based model;
- the ARIA recommendations were proposed by an expert group and needed to be validated in terms of classification and management;

Table 1. Recommendations of the ARIA workshop

1. Allergic rhinitis is a major chronic respiratory disease due to its:
   prevalence
   impact on quality of life
   impact on work/school performance and productivity
   economic burden
   links with asthma
2. In addition, allergic rhinitis is associated with sinusitis and other co-morbidities such as conjunctivitis
3. Allergic rhinitis should be considered as a risk factor for asthma along with other known risk factors
4. A new subdivision of allergic rhinitis has been proposed:
   intermittent
   persistent
5. The severity of allergic rhinitis has been classified as 'mild' or 'moderate/severe' depending on the severity of symptoms and quality of life outcomes
6. Depending on the subdivision and severity of allergic rhinitis, a stepwise therapeutic approach has been proposed
7. The treatment of allergic rhinitis combines:
   allergen avoidance (when possible)
   pharmacotherapy
   immunotherapy
   education
8. Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator
9. Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis
10. A combined strategy should ideally be used to treat the upper and lower airway diseases in terms of efficacy and safety

- new evidence-based systems are currently available to guide recommendations and include safety and costs as well as efficacy of treatments (22, 23);
- there were gaps in our knowledge in the first ARIA document. In particular:

  1 some aspects of treatment like complementary and alternative medicine were not appropriately discussed;
  2 the links between the upper and lower airways in developing countries and deprived areas were not sufficiently developed even though, in the original ARIA document, a section was written on this subject in collaboration with the UNION (formerly IUATLD);
  3 sport and rhinitis in athletes and
  4 rhinitis and its links with asthma in preschool children.

1.3. Development of the ARIA update

The ARIA update commenced in 2004. Several chapters of ARIA were extensively reviewed in an evidence-based model, and papers were published (or submitted) in peer-reviewed journals: tertiary prevention of allergy, complementary and alternative medicine, pharmacotherapy and anti-IgE treatment, allergen-specific immunotherapy, links between rhinitis and asthma and mechanisms of rhinitis (24–28).

There was then a need for a global document based on the published papers to highlight the interactions between the upper and the lower airways and to:

- develop an evidence-based global document on a key problem of respiratory medicine including diagnosis, epidemiology, common risk factors, management and prevention;
- propose educational materials for healthcare professionals and patients;
- meet the objectives of the WHO Global Alliance against Chronic Respiratory Diseases (GARD; 29) in order to help coordinate the efforts of the different GARD organizations towards a better prevention and management of chronic respiratory diseases (CRD), to increase CRD awareness and also to fill some of the gaps in knowledge;
- focus on the prevention of chronic respiratory and allergic diseases;
- highlight gaps in knowledge, particularly in developing countries and deprived areas;
- prepare an executive summary and pocket guide for doctors, patients and healthcare professionals.

2. Definition and classification of rhinitis

2.1. Introduction

Rhinitis is defined as an inflammation of the lining of the nose and is characterized by nasal symptoms including anterior or posterior rhinorrhoea, sneezing, nasal blockage and/or itching of the nose. These symptoms occur during two or more consecutive days for more than 1 h on most days (9).

Allergic rhinitis is the most common form of non-infectious rhinitis and is associated with an IgE-mediated immune response against allergens. It is often associated with ocular symptoms.

Several nonallergic conditions can cause similar symptoms: infections, hormonal imbalance, physical agents, anatomical anomalies and the use of certain drugs (30). Rhinitis is therefore classified as shown in Table 2 (1). The differential diagnosis of rhinitis is presented in Table 3 (1).

Since the nasal mucosa is continuous with that of the paranasal sinuses, congestion of the ostia may result in sinusitis which does not exist without rhinitis. The term 'rhinosinusitis' should replace 'sinusitis' (31).

Vasomotor rhinitis is a term which is not used in this document, as vasomotor symptoms can be caused by allergic and nonallergic rhinitis.

Table 2. Classification of rhinitis [from Ref. (1)]

Infectious
Viral
Bacterial
Other infectious agents
Allergic
Intermittent
Persistent
Occupational
Intermittent
Persistent
Drug induced
Aspirin
Other medications
Hormonal
Other causes
NARES
Irritants
Food
Emotional
Atrophic
Idiopathic

Table 3. Differential diagnosis of allergic rhinitis [from Ref. (1)]

Rhinosinusitis with or without nasal polyps
Mechanical factors
Deviated septum
Hypertrophic turbinates
Adenoidal hypertrophy
Anatomical variants in the ostiomeatal complex
Foreign bodies
Choanal atresia
Tumors
Benign
Malignant
Granulomas
Wegener's granulomatosis
Sarcoid
Infectious
Malignant – midline destructive granuloma
Ciliary defects
Cerebrospinal rhinorrhoea

2.2. Allergic rhinitis

Definition and classification of allergic rhinitis

- Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation.
- Allergic rhinitis is subdivided into IAR or PER disease.
- The severity of allergic rhinitis can be classified as 'mild' or 'moderate/severe'.
- Allergic rhinitis impairs QOL, sleep, school and work.
- Many nonallergic triggers induce nasal symptoms which mimic allergic rhinitis. They include drugs (aspirin and other nonsteroidal anti-inflammatory agents), occupational agents, foods, physical, emotional and chemical factors and viral infections.

2.2.1. Definition of allergic rhinitis

2.2.1.1. Clinical definition. Symptoms of allergic rhinitis include rhinorrhoea, nasal obstruction (32), nasal itching and sneezing which are reversible spontaneously or with treatment (2, 33–36). Postnasal drip mainly occurs either with profuse anterior rhinorrhoea in allergic rhinitis (37) or without significant anterior rhinorrhoea in chronic rhinosinusitis (CRS; 38, 39). Preschool children may just have nasal obstruction. However, when nasal obstruction is the only symptom, it is very rarely associated with allergy. Patients with nonallergic rhinitis may have similar symptoms (40).

Allergic rhinitis is subdivided into 'IAR' or 'PER' disease. The severity of allergic rhinitis can be classified as 'mild' or 'moderate/severe' (1).

2.2.1.2. Definition for epidemiologic studies. The clinical definition of rhinitis is difficult to use in the epidemiologic settings of large populations where it is impossible to visit everybody individually or to obtain the laboratory evidence of each immune response. However, the standardization of the definition of rhinitis in epidemiologic studies is of crucial importance, especially when comparing the prevalence between studies.

Initial epidemiologic studies have assessed allergic rhinitis on the basis of simple 'working definitions'. Various standardized questionnaires have been used for this effect (41, 42).

- The first questionnaires assessing seasonal allergic rhinitis dealt with 'nasal catarrh' (British Medical Research Council, 1960; 43) and 'runny nose during spring' (British Medical Research Council, 1962; 44).
- Questions introducing the diagnostic term of 'seasonal allergic rhinitis' were successively used: 'Have you ever had seasonal allergic rhinitis?' or 'Has a doctor ever told you that you suffer from seasonal allergic rhinitis?'
- In the European Community Respiratory Health Survey (ECRHS) full-length questionnaire, the question asked on rhinitis was: 'Do you have any nasal allergies including "seasonal allergic rhinitis"?' (45). To identify the responsible allergen, the ECRHS study has included potential triggers of the symptoms. However, this question is not sensitive enough and some patients with nonallergic rhinitis answer 'yes'.
- There are however problems with questionnaires. Many patients poorly perceive nasal symptoms of allergic rhinitis: some exaggerate symptoms, whereas many others tend to dismiss the disease (46). Moreover, a large proportion of rhinitis symptoms are not of allergic origin (47). In the Swiss Study on Air Pollution and Lung Diseases in Adults (SAPALDIA), the prevalence of current seasonal allergic

rhinitis varied between 9.1% (questionnaire answer and a positive skin prick test to at least one pollen) and 14.2% (questionnaire answer only).
- Diagnostic criteria affect the reported prevalence rates of rhinitis (48–50).
- A score considering most of the features of allergic rhinitis (clinical symptoms, season of the year, triggers, parental history, individual medical history and perceived allergy) has recently been proposed (51). Using the doctor's diagnosis (based on questionnaire, examination and skin tests to common aeroallergens) as a gold standard, these scores had good positive and negative predictive values (84% and 74%, respectively) in the identification of patients suffering from allergic rhinitis. Symptoms of perennial rhinitis have been defined as frequent, nonseasonal, nasal or ocular ('rhinoconjunctivitis').
- In one study, the length of the disease was also taken into consideration to differentiate perennial allergic rhinitis from the 'common cold' (viral upper respiratory infections; 52).

Objective tests for the diagnosis of IgE-mediated allergy (skin prick test and serum-specific IgE) can also be used (53–55). The diagnostic efficiency of IgE, skin prick tests and Phadiatop® was estimated in 8 329 randomized adults from the SAPALDIA. The skin prick test had the best positive predictive value (48.7%) for the epidemiologic diagnosis of allergic rhinitis compared to the Phadiatop® (43.5%) or total serum IgE (31.6%) (56). Future working definitions may encompass not only clinical symptoms and immune response tests, but also nasal function and eventually specific nasal challenge (57).

2.2.2. Intermittent (IAR) and persistent allergic rhinitis (PER). Previously, allergic rhinitis was subdivided, based on the time of exposure, into seasonal, perennial and occupational (9, 10, 58, 59). Perennial allergic rhinitis is most frequently caused by indoor allergens such as dust mites, molds, insects (cockroaches) and animal danders. Seasonal allergic rhinitis is related to a wide variety of outdoor allergens such as pollens or molds. However, this classification is not entirely satisfactory as:

- in certain areas, pollens and molds are perennial allergens [e.g. grass pollen allergy in Southern California and Florida (60) or *Parietaria* pollen allergy in the Mediterranean area (61)];
- symptoms of perennial allergy may not always be present all year round. This is particularly the case for a large number of patients allergic to house dust mites (HDM) suffering only from mild or moderate/severe IAR (62–65). This is also the case in the Mediterranean area where levels of HDM allergen are low in the summer (66);
- the majority of patients are sensitized to many different allergens and therefore exposed throughout the year (33, 62, 67–69). In many patients, perennial symptoms are often present and patients experience seasonal exacerbations when exposed to pollens or molds. It appears therefore that this classification is not adherent to real life;
- climatic changes modify the time and duration of the pollen season which may make predictions difficult;
- allergic patients travel and may be exposed to the sensitizing allergens in different times of the year;
- some patients allergic to pollen are also allergic to molds and it is difficult to clearly define the pollen season (70);
- some patients sensitized only to a single pollen species have perennial symptoms (71);
- due to the priming effect on the nasal mucosa induced by low levels of pollen allergens (72–77) and minimal PER inflammation of the nose in patients with symptom-free rhinitis (64, 78, 79), symptoms do not necessarily occur strictly in conjunction with the allergen season and
- nonspecific irritants such as air pollution may aggravate symptoms in symptomatic patients and induce symptoms in asymptomatic patients with nasal inflammation (80).

Thus, a major change in the subdivision of allergic rhinitis was proposed in the ARIA document with the terms 'IAR' and 'PER' (1). It was shown that the classic types of seasonal and perennial rhinitis cannot be used interchangeably with the new classification of IAR/PER, as they do not represent the same stratum of disease. Thus, 'IAR' and 'PER' are not synonymous with 'seasonal' and 'perennial' (36, 62, 67, 81–83). In the original ARIA document, the number of consecutive days used to classify patients with PER was more than four per week (1). However, it appears that patients with PER usually suffer almost every day (84).

Whereas the majority of patients have symptoms unrelated to seasons, it is possible to discriminate pollen seasons in some patients. In this case, patients experience symptoms during defined times of the year or have mild PER during most months of the year and more severe symptoms when exposed to high concentrations of allergens during pollen seasons.

As most patients are polysensitized, it appears that the ARIA classification is closer to the patients' needs than the previous one (85).

Moreover, PER does not necessarily result from allergic origin (86).

2.2.3. Severity of allergic rhinitis

2.2.3.1. Classical symptoms and signs. Allergic rhinitis is characterized by subjective symptoms which may be

difficult to quantify due to the fact that they depend largely on the patient's perception.

2.2.3.2. Symptoms associated with social life, work and school. It is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhoea and nasal obstruction. It is associated with impairments in how patients function in day-to-day life. Impairment of QOL is seen in adults (10, 87, 88) and in children (89–92). Patients may also suffer from sleep disorders and emotional problems, as well as from impairment in activities and social functioning (93).

Poorly-controlled symptoms of allergic rhinitis may contribute to sleep loss or disturbance (94–104). Moreover, H_1-antihistamines with sedative properties can increase sedation in patients with allergic rhinitis (105, 106). Although sleep apnoea syndrome has been associated with nasal disturbances (107–109), it is unclear as to whether allergic rhinitis is associated with sleep apnoea (100, 107, 110). It has been shown that patients with moderate/severe symptoms of IAR or PER have an impaired sleep pattern by comparison to normal subjects and patients with mild rhinitis (111).

It is also commonly accepted that allergic rhinitis impairs work (10, 84, 112, 113) and school performance (114–116).

In several studies, the severity of allergic rhinitis, assessed using QOL measures, work productivity questionnaires or sleep questionnaires, was found to be somewhat independent of duration (67, 84, 111, 117).

2.2.3.3. Objective measures of severity. Objective measures of the severity of allergic rhinitis include:

- symptom scores;
- visual analogue scales (VAS ; 118, 119 ; Fig. 1) ;
- measurements of nasal obstruction, such as peak inspiratory flow measurements, acoustic rhinometry and rhinomanometry (120–122);
- measurements of inflammation such as nitric oxide (NO) measurements, cells and mediators in nasal lavages, cytology and nasal biopsy (121, 123);
- reactivity measurements such as provocation with histamine, methacholine, allergen, hypertonic saline, capsaicin or cold dry air (124) and
- measurements of the sense of smell (125).

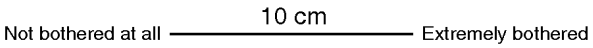

Figure 1. Mean mast cells, toludine blue staining, IgE^+ and eosinophil cell counts/mm^2 nasal biopsy tissues collected from patients with perennial allergic (PAR) and idiopathic (ID) rhinitis, and normal nonrhinitic subjects (N). (Horizontal bar + median counts; St1 = counts in epithelium; St2 = counts in superficial submucosa; St3 = counts in deep submucosa.) (Modified from Powe et al. 2001 (15) and reprinted with kind permission.)

Measurements of VAS, nasal obstruction and smell are used in clinical practice. The other measurements are primarily used in research.

2.2.3.4. ARIA classification of allergic rhinitis. In the ARIA classification, allergic rhinitis can be classified as 'mild' or 'moderate/severe' depending on the severity of the symptoms and their impact on social life, school and work (Table 4). It has also been proposed to classify the severity as 'mild', 'moderate' or 'severe' (36, 126, 127). However, it seems that this proposal makes it more complex for the practicing doctor and does not provide any significant improvement to the patient, this more complex classification failing to translate to a difference in therapeutic options.

The severity of allergic rhinitis is independent of its treatment. In asthma, the control level is also independent of asthma medications (128–132). Although such an independent relationship was suspected in a study on allergic rhinitis (67), this very important finding was confirmed in a recent study in which it was found that the severity of rhinitis is independent of its treatment (119). Thus, as for asthma, one of the problems to consider is to replace 'severity' by 'control', but sufficient data are not yet available.

2.3. Other causes of rhinitis

2.3.1. Infectious rhinitis. For infectious rhinitis, the term rhinosinusitis is usually used. Rhinosinusitis is an inflammatory process involving the mucosa of the nose and one or more sinuses. The mucosa of the nose and sinuses form a continuum and thus, more often than not, the mucous membranes of the sinuses are involved in diseases which are primarily caused by an inflammation of the nasal mucosa. For this reason, infectious rhinitis is discussed under Rhinosinusitis.

2.3.2. Work-related rhinitis. Occupational rhinitis arises in response to an airborne agent present in the workplace

Table 4. Classification of allergic rhinitis according to ARIA [from Ref. (1)]

1. 'Intermittent' means that the symptoms are present
   <4 days a week
   Or for <4 consecutive weeks
2. 'Persistent' means that the symptoms are present
   More than 4 days a week
   And for more than 4 consecutive weeks
3. 'Mild' means that none of the following items are present:
   Sleep disturbance
   Impairment of daily activities, leisure and/or sport
   Impairment of school or work
   Symptoms present but not troublesome
4. 'Moderate/severe' means that one or more of the following items are present:
   Sleep disturbance
   Impairment of daily activities, leisure and/or sport
   Impairment of school or work
   Troublesome symptoms

and may be due to an allergic reaction or an irritant response (133). Causes include laboratory animals (rats, mice, guinea-pigs, etc.; 134), wood dust, particularly hard woods (Mahogany, Western Red Cedar, etc.; 135), mites (136), latex (137), enzymes (138), grains (bakers and agricultural workers; 139, 140) and chemicals such as acid anhydrides, platinum salts (141), glues and solvents (142).

Occupational rhinitis is frequently underdiagnosed due to under-reporting and/or a lack of doctor awareness (133, 143). Diagnosis is suspected when symptoms occur in relation to work. Differentiating between immunologic sensitization and irritation may be difficult. Given the high prevalence of rhinitis in the general population, whatever the cause, then objective tests confirming the occupational origin are essential (144). Measures of inflammatory parameters via nasal lavage and the objective assessment of nasal congestion both offer practical means of monitoring responses (133). Growing experience with acoustic rhinometry and peak nasal inspiratory flow (PNIF) suggests that these methods may have a role in monitoring and diagnosing (145). The surveillance of sensitized workers may enable an early detection of occupational asthma.

2.3.3. Drug-induced rhinitis. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) commonly induce rhinitis and asthma (Table 5). The disease has recently been defined as aspirin-exacerbated respiratory disease (146). In a population-based random sample, aspirin hypersensitivity was more frequent among subjects with allergic rhinitis than among those without (2.6% *vs* 0.3%; 147). In about 10% of adult patients with asthma, aspirin and other NSAIDs that inhibit cyclooxygenase (COX) enzymes (COX-1 and COX-2) precipitate asthma attacks and naso-ocular reactions (148). This distinct clinical syndrome, called aspirin-induced asthma, is characterized by a typical sequence of symptoms: an intense eosinophilic inflammation of the nasal and bronchial tissues combined with an overproduction of cysteinyl leukotrienes (CysLT; 149) and other prostanoids (150, 151). After the ingestion of aspirin or other NSAIDs, an acute asthma attack occurs within 3 hours, usually accompanied by profuse rhinorrhoea, conjunctival injection, periorbital edema and sometimes a scarlet flushing of the head and neck. Aggressive nasal polyposis and asthma run a protracted course, despite the avoidance of aspirin and cross-reacting drugs (152). Blood eosinophil counts are raised and eosinophils are present in nasal mucosa and bronchial airways. Specific anti-COX-2 enzymes are usually well tolerated in aspirin-sensitive patients (149) but many are no longer marketed.

Table 5. List of common NSAIDs that cross-react with aspirin in respiratory reactions [from Ref. (1)]*

Generic names	Brand names
Aminophenazone	Isalgin
Diclofenac	Voltaren, Cataflam
Diflunisal	Dolbid
Etodolac	Lodine
Fenoprofen	Nalfon
Flurbiprofen	Ansaid
Ibuprofen	Motrin, Rufen, Advil
Indomethacin	Indocid, Metindol
Ketoprofen	Orudis, Oruval
Ketoralac	Toradol
Klofezon	Perclusone
Mefenamic acid	Ponstel, Mefacit
Metamizol	Analgin,
Nabumetone	Relafen
Naproxen	Naprosyn, Anaprox, Aleve
Noramidopyrine	Novalgin
Oxaprozin	Daypro
Oxyphenbutazone	Tanderil
Piroxicam	Feldene
Propylphenazone	Pabialgin, Saridon
Sulindac	Cilnoril
Tolmetin	Tolectin

* Paracetamol is well tolerated by the majority of patients, especially in doses not exceeding 1000 mg/day. Nimesulide and meloxicam in high doses may precipitate nasal and bronchial symptoms (153).

A range of other medications is known to cause nasal symptoms. These include:

- reserpine (154);
- guanethidine (155);
- phentolamine (156);
- methyldopa (155);
- ACE inhibitors (157);
- α-adrenoceptor antagonists;
- intraocular or oral ophthalmic preparations of β-blockers (158);
- chlorpromazine and
- oral contraceptives.

The term rhinitis medicamentosa (159–161) applies to the rebound nasal obstruction which develops in patients who use intranasal vasoconstrictors chronically. The pathophysiology of the condition is unclear; however, vasodilatation and intravascular edema have both been implicated. The management of rhinitis medicamentosa requires the withdrawal of topical decongestants to allow the nasal mucosa to recover, followed by treatment of the underlying nasal disease (162).

Cocaine sniffing is often associated with frequent sniffing, rhinorrhoea, diminished olfaction and septal perforation (163, 164).

Amongst the multiuse aqueous nasal, ophthalmic and otic products, benzalkonium chloride is the most common preservative. Intranasal products containing this preservative appear to be safe and well tolerated for both long- and short-term clinical use (165).

2.3.4. Hormonal rhinitis. Changes in the nose are known to occur during the menstrual cycle (166), puberty, pregnancy (167, 168) and in specific endocrine disorders such as hypothyroidism (169) and acromegaly (170).

Hormonal imbalance may also be responsible for the atrophic nasal change in postmenopausal women.

A hormonal PER or rhinosinusitis may develop in the last trimester of pregnancy in otherwise healthy women. Its severity parallels the blood estrogen level (171). Symptoms disappear at delivery.

In a woman with perennial rhinitis, symptoms may improve or deteriorate during pregnancy (172).

2.3.5. Nasal symptoms related to physical and chemical factors. Physical and chemical factors can induce nasal symptoms which may mimic rhinitis in subjects with sensitive mucous membranes and even in normal subjects if the concentration of chemical triggers is high enough (173, 174). Sudden changes in temperature can induce nasal symptoms in patients with allergic rhinitis (175). Chronic effects of cold dry air are important. Skier's nose (cold, dry air; 176) has been described as a distinct entity. However, the distinction between a normal physiologic response and a disease is not clear and all rhinitis patients may exhibit an exaggerated response to unspecific physical or chemical stimuli. Little information is available on the acute or chronic effects of air pollutants on the nasal mucosa (177).

The alterations of physiologic nasal respiration is of importance for any athlete. The impact of exercise on rhinitis and the effect of rhinitis on exercise received considerable attention before the 1984 Olympics, where evidence indicated that chronic rhinitis frequently occurs and deserves specific management in athletes (178). Athletes suffering from symptoms of rhinitis were shown to have impaired performances (179). Many active athletes suffer from allergic rhinitis during the pollen season (180, 181) and most of these receive treatment for their nasal symptoms.

On the other hand, some conditions induce nasal symptoms. This is the case of the skier's nose, a model of cold-induced rhinitis (176, 182–184), or rhinitis in competitive swimmers who inhale large quantities of chlorine gas or hypochlorite liquid (185–187). In runners, nasal resistance falls to about half of its resting values. Decongestion begins immediately after starting running and persists for around 30 min after (27).

In multiple chemical sensitivities, nasal symptoms such as impaired odor perception may be present (188).

2.3.6. Rhinitis in smokers. In smokers, eye irritation and odor perception are more common than in nonsmokers (189). Tobacco smoke can alter the mucociliary clearance (190) and can cause an eosinophilic and 'allergic'-like inflammation in the nasal mucosa of nonatopic children (191). Some smokers report a sensitivity to tobacco smoke including headache, nose irritation (rhinorrhoea, nasal congestion, postnasal drip and sneezing) and nasal obstruction (192). However, in normal subjects, smoking was not found to impair nasal QOL (193). Nonallergic rhinitis with eosinophilia syndrome (NARES) might be caused by passive smoking inducing an 'allergy-like' inflammatory response (194).

2.3.7. Food-induced rhinitis. Food allergy is a very rare cause of isolated rhinitis (195). However, nasal symptoms are common among the many symptoms of food-induced anaphylaxis (195).

On the other hand, foods and alcoholic beverages in particular may induce symptoms by unknown nonallergic mechanisms.

Gustatory rhinitis (hot, spicy food such as hot red pepper; 196) can induce rhinorrhoea, probably because it contains capsaicin. This is able to stimulate sensory nerve fibers inducing them to release tachykinins and other neuropeptides (197).

Dyes and preservatives as occupational allergens can induce rhinitis (198), but in food they appear to play a role in very few cases (195).

2.3.8. NARES and eosinophilic rhinitis. Persistent nonallergic rhinitis with eosinophilia is a heterogeneous syndrome consisting of at least two subgroups: NARES and aspirin hypersensitivity (30).

Nonallergic rhinitis with eosinophilia syndrome was defined in the early 1980s (199–201). Although it probably does not represent a disease entity on its own, it may be regarded as a subgroup of idiopathic rhinitis, characterized by the presence of nasal eosinophilia and PER symptoms of sneezing, itching, rhinorrhoea and occasionally a loss of sense of smell in the absence of demonstrable allergy. It occurs in children and adults. Asthma appears to be uncommon but half of the patients show bronchial nonspecific hyperreactivity (202). It has been suggested that in some patients, NARES may represent an early stage of aspirin sensitivity (203). Nonallergic rhinitis with eosinophilia syndrome responds usually but not always favorably to intranasal glucocorticosteroids (204).

2.3.9. Rhinitis of the elderly. Rhinitis of the elderly, or senile rhinitis as it is called in the Netherlands, is a distinctive feature in the clinical picture of an elderly patient suffering from a clear rhinorrhoea without nasal obstruction or other nasal symptoms. Patients often complain of the classical drop on the tip of the nose.

2.3.10. Emotions. Stress and sexual arousal are known to have effects on the nose probably due to autonomic stimulation.

2.3.11. Atrophic rhinitis. Primary atrophic rhinitis is characterized by a progressive atrophy of the nasal mucosa and underlying bone (205), rendering the nasal cavity widely patent but full of copious foul-smelling crusts. It has been attributed to infection with *Klebsiella ozaenae* (206) though its role as a primary pathogen is not determined. The condition produces nasal obstruction,

hyposmia and a constant bad smell (ozaenae) and must be distinguished from secondary atrophic rhinitis associated with chronic granulomatosis conditions, excessive nasal surgery, radiation and trauma.

2.3.12. Unknown etiology (idiopathic rhinitis). Sometimes termed 'vasomotor rhinitis', patients suffering from this condition manifest an upper respiratory hyperresponsiveness to nonspecific environmental triggers such as changes in temperature and humidity, exposure to tobacco smoke and strong odors.

The limited data available suggest that these patients might present with the following (207):

- nasal inflammation (in a small number of patients);
- an important role for C-fibers although direct observations explaining this mechanism are lacking;
- parasympathetic hyperreactivity and/or sympathetic hyporeactivity and/or
- glandular hyperreactivity.

Some people consider even slight nasal symptoms to be abnormal and seek consequent medical advice. Inquiry into the number of hours spent with daily symptoms may help to determine a distinction between a normal physiologic response and disease. Also, the use of a daily record card to score symptom duration and intensity, combined, if appropriate, with PNIF measurements, can provide the doctor with more insight into the severity of the disease. Marked discrepancies can be found between the description of the problem at the first visit and data from these daily measurements (208, 209).

2.4. Rhinosinusitis

Definition and classification of rhinosinusitis

- Sinusitis and rhinitis usually coexist and are concurrent in most individuals; thus, the correct terminology for sinusitis is *rhinosinusitis*.
- Depending on its duration, rhinosinusitis is classified as acute or chronic (over 12 weeks).
- Symptoms and signs overlie with those of allergic rhinitis.
- For the diagnosis of CRS (including nasal polyps, NP), an ENT examination is required.
- Sinus X-rays are not useful for the diagnosis of CRS.
- Computerized tomography scans may be useful for the diagnosis and management of CRS.

Sinusitis and rhinitis usually coexist and are concurrent in most individuals; thus, the correct terminology for sinusitis is now *rhinosinusitis*. The diagnosis of rhinosinusitis can be made by various practitioners, including allergologists, otolaryngologists, pulmonologists, primary care doctors and many others. Therefore, an accurate, efficient and accessible definition of rhinosinusitis is required.

Attempts have been made to define rhinosinusitis in terms of pathophysiology, microbiology, radiology, as well as by severity and duration of symptoms (210–212).

Until recently, rhinosinusitis was usually classified, based on duration, into acute, subacute and chronic (212). This definition does not incorporate the severity of the disease. Also, due to the long timeline of 12 weeks in CRS, it can be difficult to discriminate between recurrent acute and CRS with or without exacerbations.

Because of the large differences in technical possibilities for the diagnosis and treatment of rhinosinusitis/NPs by ENT specialists and nonspecialists, subgroups should be differentiated. Epidemiologists need a workable definition that does not impose too many restrictions to study large populations, whereas researchers need a set of clearly defined items to describe their patient population accurately. The EP^{3}OS task force attempted to accommodate these needs by allocating definitions adapted to different situations (31, 213).

2.4.1. Clinical definition. Rhinosinusitis (including NP) is an inflammation of the nose and the paranasal sinuses characterized by:

1 two or more symptoms, one of which should be nasal obstruction or discharge (anterior/posterior nasal drip):
   - blockage/congestion
   - discharge: anterior/postnasal drip (which can be discolored)
   - facial pain/pressure
   - reduction or loss of smell

The presenting symptoms of CRS are given in Table 6.

2 and endoscopic signs:
   - polyps and/or

Table 6. Presenting symptoms of chronic rhinosinusitis [adapted from Meltzer et al. (214)]

Presenting symptom	Percentage of patients with symptom (%)
Nasal obstruction	94
Nasal discharge	82
Facial congestion	85
Facial pain-pressure-fullness	83
Loss of smell	68
Fatigue	84
Headache	83
Ear pain/pressure	68
Cough	65
Halitosis	53
Dental pain	50
Fever	33

- mucopurulent discharge from the middle meatus and/or
- edema/mucosal obstruction primarily in the middle meatus.

3 and/or CT changes: mucosal changes within the ostiomeatal complex and/or sinuses.

Computerized tomography (CT) of the paranasal sinuses has emerged as the standard test for the assessment of CRS, as evidenced by the development of several CT-based staging systems. Despite its central role in the diagnosis and treatment planning for CRS, sinus CT represents a 'snapshot in time'. In CRS, the correlation between a CT scan and symptoms is low to nonexistent (215, 216). The most frequently-used scoring system for CT scans in CRS is the Lund-Mackay score (217). Overall, the Lund-Mackay score in the general population is not 0. A Lund score ranging from 0 to 5 may be considered within an incidentally 'normal' range, and should be factored into clinical decision making (218).

A proposal for the differentiation of acute and CRS has recently been published (219; Table 7).

2.4.1.1. Severity of the disease. The disease can be divided into MILD, MODERATE or SEVERE based on the total severity VAS score (0–10 cm): MILD = VAS 0–3; MODERATE = VAS 3.1–7; SEVERE = VAS 7.1–10.

To evaluate the total severity, the patient is asked to indicate on a VAS the reply to the following question (Fig. 2).

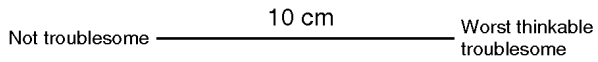

Figure 2. Effects of: (A) sympathetic innervation; (B) parasympathetic innervation; and (C) nasal reflex on nasal function.

The severity of rhinosinusitis can also be assessed by using QOL questionnaires (215, 220–227). However, these different methods of evaluation of rhinosinusitis severity are not always correlated (215, 228).

2.4.1.2. Duration of the disease. The EP^{3}OS document proposes to define the disease as acute rhinosinusitis (symptoms lasting for <12 weeks and complete resolution of symptoms) or CRS (symptoms lasting for more than 12 weeks without complete resolution of symptoms).

2.4.2. Definition for epidemiologic studies. For epidemiologic studies, the definition is based on symptomatology without ENT examination or imaging. However, a considerable overestimation of the disease can be observed when a definition of rhinosinusitis is only based on symptomatology without ENT examination or imaging (229–231).

- **Acute rhinosinusitis** is defined as:

1 a sudden onset of two or more of the following symptoms, one of which should be either nasal blockage/obstruction or nasal discharge:
   - blockage/congestion;

Table 7. Rhinosinusitis consensus research definitions and clinical trial guidelines [from Ref. (219)]

	Type of rhinosinusitis		
		Chronic rhinosinusitis	
	Acute rhinosinusitis	Without nasal polyps	With nasal polyps
Patterns of symptoms	Symptoms present for a minimum of 10 days up until a maximum of 28 days Severe disease (presence of purulence for 3–4 days with high fever) OR Worsening disease (symptoms that initially regress but worsen within the first 10 days)	Symptoms present for ≥12 weeks	
Symptoms for diagnosis	Requires Anterior and/or posterior mucopurulent drainage PLUS Nasal obstruction OR Facial pain/pressure/fullness	Requires ≥2 of the following symptoms: Anterior and/or posterior mucopurulent drainage Nasal obstruction Facial pain/pressure/fullness	Requires ≥2 of the following symptoms Anterior and/or posterior mucopurulent drainage Nasal obstruction Decreased sense of smell
Objective documentation	Requires either Nasal airway examination for mucopurulent drainage Beyond vestibule by either anterior or posterior endoscopy OR Posterior pharyngeal drainage OR Radiographic evidence of acute rhinosinusitis	Requires both Rhinoscopy to exclude polyps in the middle meatus and document presence of inflammation, such as discolored mucus or edema of the middle meatus or ethmoid area AND Evidence of rhinosinusitis on imaging (CT scan)	Requires both: Rhinoscopy to confirm the presence of bilateral polyps in the middle meatus AND Evidence of rhinosinusitis on imaging (CT scan)

- discharge: anterior/postnasal drip;
- facial pain/pressure;
- reduction/loss of smell;

2 for < 12 weeks and
3 with validation by telephone or interview.

Questions on allergic symptoms, i.e. sneezing, watery rhinorrhoea, nasal itching and itchy watery eyes, should be included.

- **Common cold/acute viral rhinosinusitis** is defined as an acute rhinosinusitis lasting < 10 days.
- **Acute bacterial rhinosinusitis** is defined by an increase in symptoms after 5 days or PER symptoms after 10 days with < 12 weeks duration.
- **Chronic rhinosinusitis/**NP is defined by:

1 the following symptoms, one of which should be either nasal blockage/obstruction/congestion or discharge (anterior/posterior nasal drip):
- discharge: anterior/postnasal drip;
- facial pain/pressure;
- reduction or loss of smell;
- nasal congestion/obstruction/blockage with
- facial pain/pressure or
- reduction/loss of smell.

2 for > 12 weeks and
3 with validation by telephone or interview.

Questions on allergic symptoms, i.e. sneezing, watery rhinorrhoea, nasal itching and itchy watery eyes, should be included.

2.4.3. Definition for research. For research purposes, acute rhinosinusitis is defined as above. Bacteriology (antral tap, middle meatal tap) and/or radiology (X-ray, CT) are advised, but not obligatory.

For research purposes, CRS is the major finding and nasal polyposis (NP) is considered a subgroup of this entity. For study purposes, the differentiation between CRS and NP must be based on endoscopy. The research definition is based on the presence of NP and prior surgery.

- **Definitions when no previous sinus surgery has been performed:**

1 Polyposis: bilateral, endoscopically visualized in the middle meatus.
2 Chronic rhinosinusitis: bilateral, no visible polyps in the middle meatus, if necessary following decongestant.

This definition accepts that there is a spectrum of disease in CRS which includes a polypoid change in the sinuses and/or middle meatus but excludes polypoid disease presenting in the nasal cavity to avoid overlap.

- **Definitions when sinus surgery has been performed**: Once surgery has altered the anatomy of the lateral wall, the presence of polyps is defined as pedunculated lesions as opposed to cobblestoned mucosa > 6 months after surgery on endoscopic examination. Any mucosal disease without overt polyps should be regarded as CRS.

2.4.4. Nasal polyposis. Nasal polyps and CRS are often considered as one disease entity, because it seems impossible to clearly differentiate both entities (58, 232–234). Nasal polyposis is considered as a subgroup of CRS.

3. Risk factors

Risk factors for allergic rhinitis

- Allergic rhinitis is a multifactorial disease induced by gene–environment interactions.
- Indoor and outdoor inhalant allergens cause allergic rhinitis.
- Major outdoor allergens include pollens and molds.
- Major indoor allergens include mites, animal danders, insects and molds.
- Food allergens are rarely the cause of isolated nasal symptoms.
- Occupational agents can cause rhinitis by allergic and nonallergic mechanisms.
- The role of indoor and outdoor air pollutants is probably of importance, but more data are needed to assess their effect.
- Socioeconomic differences are reported in allergic diseases, but more data are required before producing specific recommendations.

Risk factors for rhinitis may intervene at all ages of life and epidemiology has greatly contributed in the exploration of these factors.

3.1. Genetics and familial history

Allergic rhinitis is a multifactorial disease with genetic as well as environmental factors influencing disease development. Allergic diseases such as asthma and rhinitis have closely related phenotypes and often occur with atopy (235, 236). They show strong familial and intraindividual clustering, suggesting an overlapping disease etiology. However, some genetic polymorphisms have been associated with rhinitis alone but problems with the definition of the studied phenotypes, the small size of the population and the lack of reproductibility of the results still prevent a generalization (236–248). Over the past decade, various antigens of the HLA system have been identified as responsible for seasonal allergic rhinitis (235).

It is clear that the recent increase in the prevalence of allergic rhinitis cannot be due to a change in gene pool.

3.2. Early-life risk factors

Sensitization to allergens may occur in early life (249). However, besides allergens, early-life risk factors have rarely been related to rhinitis (250, 251). Young maternal age, markers of fetal growth (42, 252–254), multiple gestation (255–257), mode of delivery (258–262), prematurity (263), low birth weight (264, 265), growth retardation (265), hormones during pregnancy (266) and perinatal asphyxia (263) were all inconstantly related to the risk of developing allergic diseases or rhinitis. As a consequence, existing results are contradictory and require confirmation.

The month of birth has been related to allergic rhinitis but findings could have been biased because negative studies have not been published (267–271).

Several environmental co-factors and the so-called hygiene hypothesis may influence the development or prevention of allergic diseases (see 5.2.2.).

3.3. Ethnic groups

Although some studies have been carried out on asthma, fewer studies have examined the role of ethnic origins in the development of allergic rhinitis. In England, native people were at a lower risk of developing allergic rhinitis than those born in Asia or the West Indies (272). Similarly, Maori people suffered more from allergic rhinitis than New Zealanders from English origin (273). Migrants from developing to industrialized countries seem to be at risk of allergy and asthma development (274). It appears that lifestyle and environmental factors in western industrialized areas are more important than ethnicity (274–277).

3.4. Allergen exposure

Allergens are antigens that induce and react with specific IgE antibodies. They originate from a wide range of animals, insects, plants, fungi or occupational sources. They are proteins or glycoproteins and more rarely glycans as in the case of *Candida albicans* (278).

The allergen nomenclature was established by the WHO/IUIS Allergen Nomenclature Subcommittee (279). Allergens are designated according to the taxonomic name of their source as follows: the first three letters of the genus, space, the first letter of the species, space and an Arabic number. As an example, Der p 1 was the first *Dermatophagoides pteronyssinus* allergen to be identified. In the allergen nomenclature, a definition of 'major' and 'minor' allergens has been proposed. When over 50% of tested patients have the corresponding allergen-specific IgE, then the allergen can be considered as 'major'.

Most allergens have associated activities with potent biological functions and can be divided into several broad groups based either on their demonstrable biological activity or on their significant homology with proteins of a known function (280). They include enzymes, enzyme inhibitors, proteins involved in transport and regulatory proteins.

3.4.1. Inhalant allergens

3.4.1.1. The role of inhalant allergens in rhinitis and asthma. Aeroallergens are very often implicated in allergic rhinitis and asthma (281–283). They are usually classified as indoor (principally mites, pets, insects or from plant origin, e.g. *Ficus*), outdoor (pollens and molds) or occupational agents.

Classically, outdoor allergens appear to constitute a greater risk for seasonal rhinitis than indoor allergens (284), and indoor allergens a greater risk for asthma and perennial rhinitis (285). However, studies using the ARIA classification show that over 50% of patients sensitized to pollen suffer from PER (62, 67) and that, in the general population, a large number of patients sensitized to HDMs have mild IAR (62).

Although there are some concerns (286), the prevalence of IgE sensitization to indoor allergens (HDMs and cat allergens) is positively correlated with both the frequency of asthma and its severity (287–290). *Alternaria* (287, 291) and insect dusts (292, 293) have also been found to be linked with asthma and its severity as well as with rhinitis.

The complex modern indoor environment may contribute to an increasing prevalence of atopic diseases. Multiple indoor environmental allergen sources may have a synergistic effect on atopic co-morbidities (294).

Because of climatic conditions there are regional differences between allergens. It is therefore important that doctors determine the allergens of their region.

3.4.1.2. Mites

3.4.1.2.1. House dust mites. House dust mites make up a large part of house dust allergens and belong to the Pyroglyphidae family; subclass Acari, class of Arachnid, phylum of Arthropods (295, 296). The most important species are *D. pteronyssinus* (Der p), *Dermatophagoides farinae* (Der f; 297–304), *Euroglyphus maynei* (Eur m; 305–307), *Lepidoglyphus destructor* (Lep d; 308) and *Blomia tropicalis* (Blo t) particularly, but not only, in tropical and subtropical regions (306, 309–314). Most mite allergens are associated with enzymatic activities (315) which were shown to have direct nonspecific action on the respiratory epithelium (316, 317), some of which may potentiate a Th2 cell response (318).

Dermatophagoides and *Euroglyphus* feed on human skin danders which are particularly abundant in mattresses, bed bases, pillows, carpets, upholstered furniture or fluffy toys (319–325). Their growth is maximal in hot

(above 20°C) and humid conditions (80% relative humidity). When humidity is inferior to 50%, mites dry out and die (326). This is why they are practically nonexistent above 1 800 m in European mountains (327, 328) where the air is dry, whereas they are abundant in tropical mountain areas (329, 330).

Even though mites are present in the home all year round, there are usually peak seasons (65, 331, 332). Many patients have symptoms all year round but with a recrudescence during humid periods (333). However, many other patients with HDM allergy have IAR (62, 64).

House dust mite allergen is contained in fecal pellets (10–20 μm). Airborne exposure occurs with the active disturbance of contaminated fabrics and settles rapidly after disturbance.

Mite allergen in dust is associated with the prevalence of sensitization and control of the disease (334). The presence of 100 mites per gram of house dust (or 2 μg of Der p 1 per gram of dust) is sufficient to sensitize an infant. For around 500 mites or 10 μg of Der p 1 per gram of house dust, the sensitized patient shows a greater risk of developing asthma at a later date (335–337). The higher the number of mites in dust, the earlier the first episode of wheezing (336). The prevalence of sensitization to mites in the general population is more important in humid than in dry regions.

3.4.1.2.2. Other mites

Storage mites (*Glyciphagus domesticus* and *Glyciphagus destructor, Tyrophagus putrecentiae, Dermatophagoides microceras, Euroglyphus maynei* and *Acarus siro*) are present in stocked grains and flour (338). These species are abundant in the dust of very damp houses, in tropical environments where the growth of the molds increases their development and in rural habitats. These mites are particularly associated with agricultural allergies (339–342) and can induce PER symptoms (343, 344).

Other species of mites such as spider mites intervene in other professional environments [*Panonychus ulmi* in apple growers, *Panonychus citri* in citrus growers and *Tetranychus urticae* (345–350) and *Ornithonyssus sylviarum* in poultry breeders (351)]. In Korea, the citrus red mite (*P. citri*) is also a common sensitizing allergen in children living in rural areas near citrus orchards (352, 353).

3.4.1.3. Pollens. The pollen grain is the male sex cell of the vegetable kingdom. Depending on their mode of transport, one can distinguish anemophilous and entomophilous pollens. The anemophilous pollens, of a very aerodynamic form, are carried by the wind and represent a major danger as they are emitted in large quantities, can travel long distances (hundreds of kilometers) and consequently can affect individuals who are far from the pollen source. However, patients who are nearest to the emission of the pollen generally show the most severe symptoms. The entomophilous pollens are those carried by insects, attracted by colorful and perfumed flowers, from the male to the female flower. The pollens stick to the antennae of the insects. Few pollens are liberated into the atmosphere and there must be a direct contact of the subject with the pollen source to sensitize exposed subjects, as is the case with agriculturists (354) or florists (355). However, atopic patients may occasionally develop sensitization to these entomophilous pollens (356, 357). Certain pollens such as dandelion are both entomophilous and anemophilous.

The capacity for sensitization to pollens is theoretically universal, but the nature and number of pollens vary with the vegetation, geography, temperature and climate (61, 358–360). There are important regional differences. Most patients are sensitized to many different pollen species (361). Surprisingly, pollen sensitization is lower in rural than in urban areas, whereas the pollen counts are higher in the country (362). The pollens causing the most common allergies are:

- grasses that are universally distributed. The grasses pollinate at the end of spring and beginning of summer, but, in some places such as Southern California or Florida, they are spread throughout the year. Bermuda grass (*Cynodon dactylon)* and Bahia grass (*Paspalum notatum*) do not usually cross-react with other grasses (363);
- weeds such as the Compositeae plants: mugwort (*Artemisia*) and ragweed (*Ambrosia*; 364–366), *Parietaria*, not only in the Mediterranean area (367–373), *Chenopodium* and *Salsola* in some desert areas (374), weeds such as ragweed flower at the end of summer and beginning of autumn. *Parietaria* often pollinates over a long period of time (March–November) and is considered as a perennial pollen;
- and trees: the birch (*Betula*), other Betulaceae (375–381), Oleaceae including the ash (*Fraxinus*) and olive tree (*Olea europea*; 382–384), the oak (*Quercus*), the plane tree (*Platanus*; 385, 386) and Cupressaceae including the cypress tree (*Cupressus*; 387–392), junipers (*Juniperus*; 393), thuyas (394), the Japanese cedar (*Cryptomeria japonica*; 395) and the mountain cedar (*Juniperus ashei*; 396, 397). Trees generally pollinate at the end of winter and at the beginning of spring. However, the length, duration and intensity of the pollinating period often vary from one year to the next, sometimes making the diagnosis difficult. Moreover, the change in temperature in Northern Europe has caused earlier birch pollen seasons (398). Multiple pollen seasons in polysensitized patients are important to consider.

The size of the pollen varies from 10 to 100 μm on average. This explains their deposition in the nostrils and, more particularly, the eyes. Most pollen-allergic patients suffer from rhinoconjunctivitis. However, pollen allergens

can be borne on submicronic particles (399, 400) and induce and/or contribute to the persistence of rhinitis and asthma. This is particularly the case of asthma attacks occurring during thunderstorms (401–405).

Cross-reactivities between pollens are now better understood using molecular biology techniques (406–409). However, it is unclear as to whether all *in vitro* cross-reactivities observed between pollens are clinically relevant (410). Major cross-reactivities include pollens of the Gramineae family (411–413) except for Bermuda (414, 415) and Bahia grass (416), the Oleaceae family (382, 417, 418), the Betulaceae family (419, 420) and the Cupressaceae family (421) but not those of the Urticaceae family (422, 423). Moreover, there is clinically little cross-reactivity between ragweed and other members of the Compositeae family (424–426).

3.4.1.4. Animal danders

3.4.1.4.1. Cat and dog allergens. The number and variety of domestic animals have considerably increased over the past 30 years, especially in urban environments of western countries. It is estimated that in many European countries, as many as one in four residences possesses a cat. Dogs are found in even greater numbers. The danders and secretions carry or contain powerful allergens capable of causing allergic reactions (427).

Cats and dogs produce major allergens in asthma, rhinitis or rhinoconjunctivitis, cough, but also, more rarely, in urticaria and angioedema.

The principal sources of cat allergen are the sebaceous glands, saliva and the peri-anal glands, but the main reservoir is the fur. The major cat allergen (Fel d 1) is transported in the air by particles inferior to 2.5 μm (428) and can remain airborne for long periods. Fel d 1 is also adherent and can contaminate an entire environment for weeks or months after cessation of allergen exposure (429). It sticks to clothing and can be carried out to areas in which the pet has no access. Fel d 2 is another important allergen.

The major dog allergen (Can f 1) is principally found in the dog's fur and can also be found in the saliva (430), skin and urine (431). This allergen can be transported in airborne particles.

Cat and dog allergens are present in high amounts in domestic dust, upholstered furnishings and to a lesser degree in mattresses (432, 433). Moreover, they can be found in various environments where the animals do not live such as day care centers (434, 435), schools (436), public transportation (437), hospital settings (324, 438, 439) and homes without animals (440). Schools represent a particular risk environment for children allergic to cats as they may develop or worsen symptoms (441), and are a site for the transfer of cat allergen to homes (442). The low level of cat allergen that exists in many homes without cats is capable of inducing symptoms in very sensitive patients (443).

Patients allergic to cats and dogs frequently display IgE reactivity against allergens from different animals (444, 445). Albumins have been recognized as relevant cross-reactive allergens (446). Moreover, there are common, as well as species-restricted, IgE epitopes of the major cat and dog allergens (447).

3.4.1.4.2. Rodents. Rabbits (*Oryctolagus cuniculus*, Ory c) and other rodents such as guinea pigs, hamsters, rats (*Rattus norvegicus*, Rat n), mice (*Mus musculus*, Mus m) and gerbils are potent sensitizers. The allergens are contained in the fur, urine (134), serum (448) and saliva. Cross-sensitizations between rodents are common.

These animals can determine occupational sensitization in laboratory personnel (10–40% of the exposed subjects; 449) and in children of parents occupationally exposed to mice, rats and hamsters (450–452). Rodent allergens are common in houses either from pets or due to contamination by mouse urine in deprived areas. Exposure to mouse allergen induces high sensitization prevalence in inner-city home environments (453).

Subjects can become sensitized to rodents in less than a year when directly exposed to the animals.

3.4.1.4.3. Other animals. Most patients allergic to horses (*Equus caballus*, Equ c) initially develop nasal and ocular symptoms but severe asthma exacerbations are not uncommon. The allergens are very volatile and sensitization may occur by direct or indirect contact (454). The allergens are found in the mane, transpiration and urine. The major allergen of horse dander is Equ c1 (455, 456). Cross-sensitization can sometimes be found with other equidae (pony, mule, donkey and zebra) and with cat, dog and guinea pig albumins.

Allergy to cattle (*Bos domesticus*, Bos d) has decreased due to the automation of cattle breeding and milking but it still remains present in cattle-breeding areas (457–459).

3.4.1.5. Fungal allergens

3.4.1.5.1. Molds. Superior fungus, mold and yeast are plants which do not possess chlorophyll but which liberate large quantities of allergenic spores into indoor and outdoor environments. Mold spores make up an allergen source whose importance is significantly related to an increase in the hospitalization of asthmatics (460–462). Widespread in the air and resulting from putrefying organic matter, fungi and molds are present everywhere except in the case of low temperatures or snow, where their growth is hindered. Their development is especially increased in hot and humid conditions, which explains their seasonal peaks and abundance in certain hot and humid areas.

The mold spores are small in size (3–10 μm) and penetrate deeply into the respiratory tract. They can provoke rhinitis as well as asthma. For reasons which are

unknown, children are more often sensitized to mold than adults (463).

Three important types of mold and yeast can be distinguished depending on their origin (464):

- The principal atmospheric (outdoor) molds are *Cladosporium* (465, 466) and *Alternaria* (467–470) with a peak during the summer, and *Aspergillus* and *Penicillium* which do not have a defined season. Large regional differences are found (471–477).
- Domestic (indoor) molds are also very important allergens (474, 476, 478, 479). Microscopic fungus present in the home is capable of producing spores all year round and is responsible for PER symptoms, especially in a hot and humid interior. Indoor molds have been associated with dampness (480–483). They can also grow in aeration and climatization ducts (central heating and air conditioning) and in water pipes. They are particularly abundant in bathrooms and kitchens. Molds also grow on plants which are watered frequently or on animal or vegetable waste, furnishings, wallpaper, mattress dust and fluffy toys.
- Molds can be naturally present in foods (*Penicillium, Aspergillus* and *Fusarium* and, more rarely, *Mucor*) and in additives when used in the preparation of numerous foodstuffs. However, it is difficult to define the allergenic role of these alimentary molds.

3.4.1.5.2. Yeasts. The yeasts reputed to be the most allergenic are *C. albicans, Saccaromyces cerevisiae* and *Saccaromyces minor* (484) and *Pityrosporum* (485). Immunoglobulin E-mediated sensitization to yeasts has been shown, particularly in atopic dermatitis (485–488). Most yeasts present cross-reactive antigens (489). Yeast can be found in foods and in the atmosphere. *Sporobolomyces* is responsible for asthma and rhinitis (490).

3.4.1.5.3. Basidiomycetes and Ascomycetes. Their spores are found in large quantities in the atmosphere and can be allergenic in patients with asthma and rhinitis (491, 492) but their role as an atmospheric allergen is still difficult to define. However, cases of occupational allergies to superior fungal spores are not rare (493).

3.4.1.6. Insects. The inhalation of insect waste can induce an IgE immune response and respiratory allergies. Certain allergens, such as haemoglobin or tropomyosin of diptera, have been identified (494–496).

Insect allergens can be found indoors [cockroaches (293) or Chiromides in some tropical areas like the Sudan (497, 498)] or induce sensitization after occupational exposure (e.g. experimental work with crickets; 499–501). However, the concentration in allergens needs to be very high to bring about a sensitization.

Cockroach allergen is found in gastrointestinal secretions as well as on the chitin shell. The allergen is distributed in large particles that do not become airborne. Cockroaches tend to cluster in hiding places and forage in the dark. Seeing cockroaches during the day suggests that they are present in very large numbers. The allergen is usually distributed throughout an infested home (502). Elevated concentrations have been observed in high-rise apartments, urban settings, pre-1940 constructions and households with low income (503–505). Cockroaches are particularly important in low-income housing ('inner city') where they can cause severe asthma (292). In certain hot and humid regions of the United States (506, 507) or tropical areas such as South East Asia (508–510), allergies to cockroaches are as frequent or even more frequent than allergies to ragweed pollen or to HDMs. However, cockroaches are also prevalent in many European countries (511–513) and even in Nordic countries (514).

3.4.1.7. Other inhalants. The allergenic role of **bacteria** is difficult to evaluate. At the present stage of our knowledge, it can be estimated that asthma or rhinitis brought about by a bacterial allergy is exceptional, even though a specific IgE to bacteria has been found. However, the enzymes originating from bacteria and used in the industrial environment (e.g. detergents) can cause asthma or rhinitis with a high prevalence (515, 516).

Ficus benjamina, known as Java willow, Ceylon willow or Bali fig tree, is a tropical nonflowering plant used ornamentally in many homes and public places. Inhalant allergy to *Ficus* has been reported (517) and appears to be relatively common, probably because *Ficus* allergens are cross-reactive with those of latex (518). The allergens originally located in the sap of the plant are also present in dust collected from the leaf surfaces and in house dust on the floor where the allergen may persist for months after removal of the plant (519). Other ornamental plants may also be potent allergens (520).

3.4.2. Food allergens. Food allergy is rare in subjects with allergic rhinitis but without other symptoms. On the other hand, rhinitis is a common symptom of food allergy in patients with multiple organ involvement. In infants under 6 months, the majority of allergic reactions are due to milk or soya. Over 50% of infants with cows' milk allergy suffer from rhinitis (521). In adults, the most common food allergens causing severe reactions are peanuts (522), tree nuts, fish, crustacea, eggs, milk, soyabeans, sesame, celery and some fruits like apples and peaches (for review see Ref. 523).

Pollinosis patients often display adverse reactions upon the ingestion of plant-derived foods as a result of IgE cross-reactive epitopes shared by pollen and food allergen sources. The symptoms of such pollen–food syndromes range from local oral allergy syndrome to severe systemic anaphylaxis (524–526). The best known association is between birch pollen and a series of fruits (including apple), vegetables and nuts (419, 527–532). Other associations include celery–mugwort–spice (533–535), mugwort–mustard, mugwort–peach, ragweed–melon–

banana (536), grass–melon (537), plantain–melon, *Parietaria*–pistachio, Russian thistle–saffron, peach–cypress (538) and Japanese cypress–tomato (539). An association between grass pollen and peanut allergy was recently suggested (540) but needs confirmation. On the other hand, clinically insignificant cross-reactivity exists among cereal grains and grass pollens (541).

Cross-reactive antigens have been identified between latex and banana, chestnut or kiwi fruit (542, 543). Although it is common to find positive skin tests and IgE antibodies to a range of legumes in peanut allergic patients, except for lupine (544), only a small percentage of the individuals also have clinical responses which are almost always less severe than to the peanut itself (545).

Molecular biology-based approaches have also improved our knowledge on cross-reactivity among allergens (546–548). The identification of allergens in fruits and vegetables showed IgE cross-reactivities with the important birch pollen allergens Bet v 1 (549) and Bet v 2 (birch profilin; 550–553). Many other cross-reactive antigens have also been identified and characterized. Dependent on the main cross-reactive allergen, different symptoms may be observed. Bet v 1 in apples, cherries, peaches and plums mainly causes mild symptoms such as the oral allergy syndrome (554). However, Bet v 1 associated with other allergens may cause generalized symptoms. Sensitization to Bet v 2 is more often associated with generalized symptoms, in particular urticaria and angioedema (555). Lipid-transfer proteins are relevant pan-allergens of fruits and vegetables (556, 557).

3.4.3. Occupational agents. Occupational airway diseases (OAD) include asthma, rhinitis, chronic obstructive pulmonary disease (COPD) and chronic cough (Fig. 3). Pneumoconiosis and fibrosis are other occupational respiratory diseases but are not included in OAD. There are many overlaps between the four diseases and it may be difficult to make a clear distinction between them. Moreover, many patients suffering from occupational and non-OADs are exposed to a number of risk factors and it may not be easy to demonstrate the occupational origin of the disease.

3.4.3.1. Classification and definition. **Work-related rhinitis and asthma** refer to at least two nosologic entities (558):

- occupational rhinitis and/or asthma 'caused' by the workplace (133, 559). Occupational agents can then be sensitizing (allergens), irritant or both;
- and asthma or rhinitis which worsen at work due to other causes (work-aggravated or exacerbated asthma; 84, 560–562) and
- in many cases, and particularly for high-molecular-weight agents, occupational rhinitis precedes asthma (133, 559).

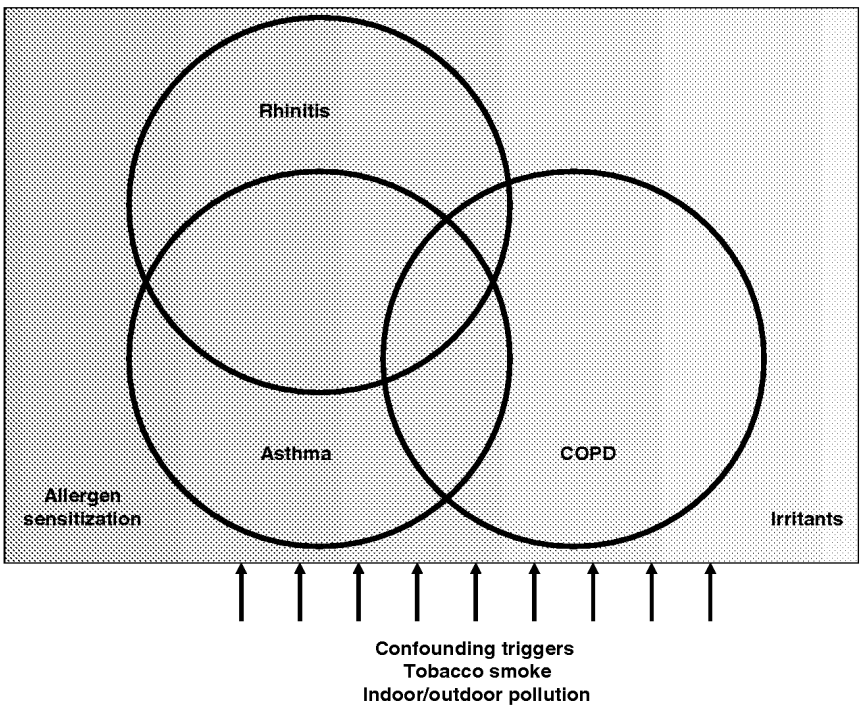

Figure 3. Effect of repeated provocation with capsaicin or placebo on nasal complaints in idiopathic rhinitis patients, as indicated by a symptom score measured on a VAS of 0–10 cm. (Modified from Blom et al. 1997 (23) and reprinted with kind permission.)

Work-related chronic cough is often associated with asthma or COPD, but when it is the only symptom, it represents a prevalent work-related airway disease (563, 564).

Chronic obstructive pulmonary disease does not have a clinical subcategory that is clearly identified as occupational, largely because the condition develops slowly and several risk factors (in particular tobacco smoking) are concomitant (565). However, some patients may have rhinitis, asthma and COPD at a varying degree due to the interaction of multiple occupational agents and co-factors such as tobacco smoke and outdoor and indoor air pollution, in particular biomass fumes in developing countries.

3.4.3.2. The most common occupational agents inducing rhinitis and asthma. In most countries, the same occupational agents are the most common causes of asthma and rhinitis (566, 567–569). These include: isocyanates (570), flour and grain, wood dust (135, 571, 572), glutaraldehyde and anhydrides (573), solder/colophony (574–576), laboratory animals, insects (577), resins and glues (578), latex (137), metal salts (141) and persulfates (579, 580).

Small mammals can determine occupational sensitization in laboratory personnel (10–50% of the exposed subjects; 449, 581). Two distinguishable syndromes have been identified (582). The first is characterized by rhinitis with negative skin prick tests. The second consists of rhinitis leading progressively to asthma with positive prick tests. Atopy (451, 452) and active smoking (583) represent a risk for the development of laboratory animal allergy. Prick tests are useful diagnostically only in the latter. Moreover, the prevalence of allergy to laboratory animals is quite high.

Industrially-used natural rubber latex is obtained from *Hevea brasiliensis* (Euphorbiaceae family). Whereas the chemical additives used in latex manufacture are a cause of delayed-type hypersensitivity (allergic contact dermatitis; 584), IgE-mediated allergy to natural rubber latex proteins (latex allergy) is a serious health issue in healthcare workers (137, 585) and other occupations. Symptoms of latex allergy include contact dermatitis, rhinitis and asthma and, more occasionally, anaphylaxis (137, 586). Skin tests and serum-specific IgE can be used for the diagnosis of latex allergy (587, 588). If needed, provocative challenge can be carried out.

Bakers often have rhinitis and asthma (139, 589, 590). Immunoglobulin E sensitization to bakery allergens (flour; 139, 591) or enzymes (592) or contaminants (593) seems to be the main cause of bakers' asthma and rhinitis but cannot explain nasal or bronchial symptoms in each case (594). Occupational rhinitis, both IgE and non-IgE-mediated, is associated with asthma symptoms (595). Bronchial responsiveness to bakery-derived allergens is strongly dependent on specific skin sensitivity (596). There may be interactions with tobacco smoking (597).

Many other high-molecular-weight allergens can induce IgE-mediated rhinitis and asthma: agricultural mites (339–342, 347, 348, 350, 351), coffee beans (598), proteolytic enzymes (515, 599, 600), other enzymes (601, 602), insect dust (577); plants and flowers (603, 604).

Low-molecular-weight agents represent at least 50% of occupational asthma agents, but the mechanisms of the reactions are still poorly understood (605–607). Although these can act as reactive haptens, nonimmunologic mechanisms are common (608). An IgE-mediated sensitization is clear for some agents, but IgG subclasses and IgG_4 are also increased as a consequence of the exposure, the disease or both (605). Many occupational agents inducing rhinitis and asthma are isocyanates (570, 609), aldehydes (610), anhydrides (573), ninhydrin (611), pharmaceutical compounds (612) or others (613). However, more than 250 different chemical entities have been identified. Some compounds like chlorine can induce irritant rhinitis in 30–50% of exposed workers (173, 174).

Formaldehyde is a small volatile chemical widely used in industry and as a sterilizing agent in medicine. At high concentrations, it is toxic and can induce irritative side effects, but it acts as a reactive hapten and can become allergenic usually leading either to IgE-mediated reactions or contact dermatitis. However, IgE-mediated allergic reactions appear to be related mostly to the pharmaceutical use of formaldehyde (614, 615). In homes, schools or occupational settings, formaldehyde acts mainly as an irritant (616, 617) but not always (618, 619).

3.4.3.3. Problems specific to developing countries. For several years, miners and founders have been known to suffer from pneumoconiosis, often associated with tuberculosis and tobacco smoking (620–623).

More recently, asthma, COPD, chronic cough and/or rhinitis induced by occupational exposure have been identified in developing countries (591, 624–638).

The same agents of occupational asthma are found in developed and developing countries (639–641), but some agents are specific to developing countries, and the levels of exposure are not usually controlled, making the diseases more prevalent and severe than in developed countries. Tobacco smoking, air pollution and possibly tuberculosis and its sequelae (not demonstrated for asthma) were found to be confounding factors.

3.5. Pollutants

Up to 1970, in Europe and the USA, episodes of atmospheric winter pollution were frequently responsible for acute mortality epidemics by cardiovascular and respiratory diseases. The responsibility for such effects was given to high concentrations of sulphur dioxide (SO_2) and particulate matter (PM) in the air of cities, usually due to unfavorable meteorological conditions and air stagnation. There has been a significant reduction of industrial pollution in western countries with the use of efficient filters in factory chimneys, and with combustibles such as petrol and electricity which pollute less than coal. Urban air pollution is still highly prevalent in some developing

countries and in a few developed ones. Moreover, urban-type pollution is still of major concern in Western countries with an increase in automobile-induced pollution.

Throughout the world, indoor air pollution, tobacco smoking and occupational exposures are of great concern. Augmented reactivity to irritants is a phenotypic characteristic of both nonallergic and allergic rhinitis, but the role of pollution in rhinitis is still a matter of debate.

3.5.1. Outdoor pollutants in allergic rhinitis

3.5.1.1. Pollution, IgE sensitization and rhinitis prevalence. Cross-sectional epidemiologic studies have demonstrated that allergic rhinitis in general (642, 643), and pollinosis to Japanese cedar pollen in particular (644, 645), are more prevalent in subjects living in areas of heavy automobile traffic. Sensitization to pollen was found to be increased in relation to truck but not car traffic (646). Some studies found that exposure to outdoor air pollutants may increase the risk of allergic rhinitis (647–650), whereas others did not find any relationship (651). Outdoor pollutants were also associated with an increase in rhinitis of undefined origin (652–655). However, many studies showing the effects of air pollution on health rely on self-reported exposure, which may be inaccurate (656, 657). The results of these studies are inconsistent and warrant further attention.

Fossil fuel combustion products may act as adjuvants in the immune system and may lead to an enhancement of allergic inflammation (658). Through this mechanism, diesel exhaust may be a contributor to the increased prevalence and morbidity of asthma and allergic rhinitis. Diesel exhaust particles were shown to skew the immune response towards IgE production (659) and augment allergic inflammation (660–662). Nasal challenge with diesel exhaust particles induces alterations in cytokine responses and an increase in IgE production (663). Diesel exhaust particles can induce allergic diseases with an increased IgE production and a preferential activation of Th2 cells (664–666). They may also act as an adjuvant of pollen allergens (667). Metabolic and cellular activation pathways were linked to chemicals such as polycyclic aromatic hydrocarbons contained in diesel exhaust particulates (668).

3.5.1.2. Automobile pollution and nasal symptoms. The principal atmospheric pollutants emitted by automobiles can be classified as follows:

1. Oxidant pollutants which are chemically evolving in the troposphere due to the sun rays:
   - **Carbon monoxide (CO)**, a result of incomplete coal combustion, but with no apparent involvement in rhinitis.
   - **Nitric oxides (NO_x)** and especially NO and NO_2, a result of nitrogen oxidation in the air at high temperatures. In Swiss preschool children, symptoms of irritation of the upper respiratory tract were increased in the zones of high NO_2 concentrations (669).
   - **Volatile organic compounds (VOC)** including hydrocarbons and some oxygen composites. The formed secondary pollutant is, above all, **ozone** (670) but there are also other species of oxidants (peroxyacetylnitrates, aldehydes, nitric acid, oxygen peroxide, etc.). The production of ozone is maximal in steep-sided or very sunny geographical sites such as Southern California (671), Switzerland, Austria, Germany, the South of France and around large cities. The ozone peaks occur from April to September in the Northern Hemisphere. Nearly 40% of the inhaled ozone is absorbed by the nasal mucosa. Ozone challenge results in nasal inflammation and congestion (672–675). It increases the late-phase response to nasal allergen challenge (676). Long-term ozone exposure in children (677) showed acute inflammation of the nasal mucosa after the first ozone peak and possible adaptation of the mucosa during the summer season. Chronic exposure to high levels of ozone was not found to induce nasal symptoms in children but increased bronchial hyperreactivity (678).
2. Sulphur pollutants, such as SO_2 formed from diesel sulphur. High levels of SO_2 sign acid-particulate pollution of industrial origin in relation to the combustion of coal and fuels which are rich in sulphur. Exposure to SO_2 decreases the secretion of nasal mucus and increases the resistance of the nasal airways (679, 680).
3. Organic chemical agents which include polyaromatic hydrocarbons, such as benzo(a)pyrene, benzo(k)fluoranthene, benzo(b)fluoranthene, benzo(g,h,i)pirylene and benzo(a)anthracene. Even though formaldehyde and VOC are mainly indoor pollutants, they are detectable in some cities, such as Los Angeles, at concentrations able to induce irritating symptoms of the upper respiratory tract (681).
4. Carbon dioxide (CO_2) produced by the oxidation of the carbon of the fuels.
5. Metals (notably lead), present initially in oils and fuels.
6. Particles (PM) which are produced mainly by the incomplete combustion of the fuels and lubricants. They can be classified according to their diameter: PM 10 (<10 μm), PM 2.5 (<2.5 μm) and nanoparticles (<1 μm). The finer the particles, the deeper they penetrate into the respiratory tract and the more capable they are of passing through the air–blood barrier (682). Some studies have found that subjects exposed to PM10 had more upper respiratory symptoms than those exposed to lower levels (683, 684). PM2.5 can induce nasal eosinophilia (685).

In developing countries, automobile pollution in large cities is becoming a major problem because of the

increased traffic and the level of maintenance of vehicles which emit very large quantities of pollutants.

3.5.1.3. Acute effects of outdoor air pollution. Acute effects due to the outdoor exposure to certain gases/fumes and PM have not been sufficiently studied with regards to nasal symptoms. The few available studies inconsistently suggest an increase in rhinitis symptoms or consultations for allergic rhinitis during peaks of pollution (686–688). Pollution and meteorological factors are closely related to complaints of nonallergic, noninfectious perennial rhinitis patients (689).

3.5.1.4. Chronic effects of outdoor air pollution. The chronic effects of atmospheric pollutants have been studied, but, except for the known effects of PM on the lower airways, no definite conclusion can be drawn (690).

Pollution is an important cause of nasal symptoms in nonallergic subjects as demonstrated in Mexico City (177, 691, 692).

In one study, patients living in congested areas due to automobile traffic had more severe symptoms of rhinitis and conjunctivitis than those living in uncongested areas (693). Outdoor pollution appears to induce symptoms in patients with allergic rhinitis (174, 651, 694).

3.5.2. Indoor air pollution

3.5.2.1. Developed countries. Indoor air pollution is of great importance since subjects in industrialized countries spend over 80% of their time indoors. It includes domestic allergens and indoor gas pollutants (695–698), among which tobacco smoke is the major source (699).

Other pollutants may play a role, especially when a fuel or wood-burning stove is present in the house (700–702) with the emission of carbon oxides, NO, PM, VOC and SO_2. In some studies, household wood or coal stove use was negatively associated with atopic sensitization and allergic rhinitis in childhood (703) but this was mainly confounded by childhood residential environments, especially the farm environment (704).

Gas cooking may also be involved in respiratory symptoms (705), especially in women and atopic subjects (706).

Certain furniture can also liberate compounds utilized during the manufacturing process (plywood, glue, fabric, emitting formaldehydes and isocyanates; 617). However, in these studies, nasal symptoms were not usually examined. An association between asthma and allergic symptoms and phthalates in house dust has been found in children (707).

3.5.2.2. Developing countries. Biomass fuels represent a major danger in developing countries. However, over 2 billion people, almost all in developing countries, rely on coal and biomass in the form of wood, dung and crop residues for domestic energy (708, 709). These materials are typically burnt in simple stoves with a very incomplete combustion. Consequently, women and young children are exposed to high levels of indoor air pollution every day, resulting in an estimated 1.5–2.0 million premature deaths a year and a high prevalence of COPD (698, 710). Little information is available for allergic rhinitis. However, in Ethiopia, an increased risk of allergy was associated with the use of biomass fuel and particularly kerosene in the home (711).

3.5.3. Tobacco smoke

3.5.3.1. IgE sensitization. Many patients with allergic rhinitis smoke. Smoking inconstantly increases total and specific IgE (712–716) and the IgE sensitization to some occupational allergens (717–719). However, in the absence of longitudinal studies, it is difficult to establish whether smoking is a causative factor of allergy or not (714, 720).

Prenatal (252, 721) and early postnatal exposure to tobacco smoke enhances allergic sensitization in some groups of subjects such as boys (722) during the first 3 years of life.

Few studies have examined the relationship between tobacco smoking and the prevalence of rhinitis (55, 715, 723–729). In three studies, the prevalence of self-reported nasal allergy symptoms was lower in smokers than in nonsmokers (55, 715, 723). In one study involving adolescents, smoking was found to increase the prevalence of rhinoconjunctivitis (729). On the other hand, there was no effect of environmental tobacco smoke (ETS) exposure at home, neither on allergic sensitization nor allergic rhinitis (730).

3.5.3.2. Effects of tobacco smoke on nasal symptoms. In smokers, eye irritation and odor perception are more common than in nonsmokers (189). Moreover, some smokers report sensitivity to tobacco smoke including headache and nose irritation (rhinorrhoea, nasal congestion, postnasal drip and sneezing; 192). The more the subjects smoke, the more they report chronic rhinitis (731). Objective assessments have confirmed that smoke-sensitive patients experience rhinorrhoea and/or nasal obstruction when challenged with tobacco smoke (732). Tobacco smoke does not appear to be allergenic in contradistinction to tobacco leaves in exposed workers (733, 734). Tobacco smoke can alter the mucociliary clearance (190) and can cause an eosinophilic and 'allergic'-like inflammation in the nasal mucosa of nonatopic children (191). In some rhinitis patients, tobacco smoking or passive smoking can induce a nasal reaction interfering with allergens and inducing symptoms of rhinitis (735). However, in normal subjects, smoking does not impair nasal QOL (193).

Passive smoking may be associated with nasal symptoms but studies do not always accord. In Trinidad and Tobago, smoking at home is strongly associated with symptoms of asthma and rhinitis in children of primary

school age (736). A substantial number of women experience nasal symptoms with ETS exposure (737).

It is not yet known whether tobacco smoke may affect the response to intranasal glucocorticosteroids.

3.5.4. Climatic change impacts allergens. Climate change impacts aeroallergens, particularly pollens (738) and molds (739). The timing of tree pollen seasons is known to depend mostly on a nonlinear balance between the winter chilling required to break dormancy and spring temperatures. A shift in the timing of birch pollen seasons was found in Europe due to warming but there are regional contrasts, the season being earlier or later (398, 740). In Spain, it has been predicted that in 100 years, oak trees will pollinate one month earlier due to climate change (741). However, similar findings have been observed for grass pollens (742). The duration of the pollen season is extended in some species. Moreover, plants produce a greater quantity of pollen under these changed climatic conditions (743, 744). Stronger allergenicity is observed in the pollen from trees grown at increased temperatures or in polluted areas (745–748). Climate changes are blamed for the increase in allergic diseases (738, 749).

3.6. Social class

Socioeconomic differences in allergic disease prevalence have been reported; asthma and in particular severe asthma have been associated with poverty in the United States (750) and hay fever and eczema with relative affluence in developed (721, 751, 752) and developing countries (753). In the inner city of the USA, low social class was univariately associated with increases in total IgE, the number of allergen sensitizations and levels of specific IgE (504). It is not yet established as to what degree such differences in disease prevalence reflect patterns of sensitization and specific allergen sensitivities. Moreover, in longitudinal studies, it has been found that the role of social class has changed over time. The steepest increase in asthma and allergic rhinitis occurred in conscripts with a low socio-economic status (752).

In Nottingham, in a study of 2 114 individuals, those with perennial symptoms were no more likely to have been working in a dusty or smoky environment (754).

4. Mechanisms

4.1. Allergic inflammation

Allergic rhinitis is classically considered to result from an IgE-mediated allergy associated with a nasal inflammation of variable intensity (755). Cells, mediators, cytokines, chemokines, neuropeptides, as well as adhesion molecules and cells all cooperate in a complex network provoking specific symptoms and nonspecific nasal hyperreactivity. The understanding of the mechanisms of disease generation provides a framework for rational therapy in this disorder, based on the complex inflammatory reaction rather than on the symptoms alone.

4.1.1. IgE-dependent mechanisms. Allergy is generally caused by a sustained overproduction of IgE in response to common environmental antigens such as indoor and outdoor allergens, foods and other allergens (756). Immunoglobulin E itself constitutes a very minute fraction of the total antibody in the human serum (50–300 ng/ml of IgE *vs* 10 mg/ml of IgG). However, the biological activities of IgE are powerfully enhanced by the activities of the specific cell surface receptors to which it binds, which may be of the high or low affinity phenotype.

Immunoglobulin E production results from complex interactions between B-cells, T-cells, mast cells and basophils, involving the presence of the cytokines interleukin (IL)-4, IL-13 and IL-18, as well as a physical interaction between T and B-cells by a number of surface and adhesion molecules (757). Th2-cells (758) and a downregulation of T-regulatory cell 1 responses (759, 760) drive the synthesis of IgE and the recruitment, maturation, survival and effector function of accessory cells such as eosinophils, basophils and mast cells.

Local IgE production has been a contentious concept for over 40 years. For a long time, IgE-producing B-cells were observed in local lymphoid tissue. However, it has been shown that IgE is produced in the local lymphoid tissues and locally in both the nasal and bronchial mucosa (761, 762). PER IgE synthesis takes place in the nasal mucosa during and just after the pollen season (763). Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis (764).

Allergen-specific IgE, synthesized in response to allergens in the environment, becomes fixed to FcεRI on the membranes of mast cells and basophils. Mast cell accumulation in the airway mucosa is an important pathophysiologic event in allergic rhinitis and asthma, as inhaled allergens impact the mucosal surfaces of the nose and/or lungs. The aggregation of receptor-bound IgE molecules on exposure to specific allergen results in the production of mediators (histamine, leukotrienes and others) that produce the allergic response (765). The immediate response depends on the structure of the target organ: typically, itching, sneezing, rhinorrhoea and blockage in the nose, with bronchoconstriction and wheeze due to smooth muscle contraction in the lungs (766). Late-phase allergic reactions and chronic inflammatory changes in the asthmatic lung involve many cell types including T-cells, mast cells and eosinophils (767). The links between an IgE-mediated reaction and rhinitis or asthma have been confirmed by the effect of an anti-IgE monoclonal antibody in these diseases (768–771).

4.1.2. Non-IgE-dependent mechanisms. However, it is now also appreciated that allergens, on account of their enzymatic proteolytic activity, may directly activate

epithelial cells (318, 772, 773) and eventually lead to a Th2-immune response, inducing cytokine and chemokine release (774), thus having the potential to induce airway inflammation independent of IgE (775). Moreover, Der p 1 is able to alter the epithelial tight junctions (316), thereby increasing epithelial permeability (776). The relative importance of non-IgE- to IgE-mediated mechanisms is undetermined.

4.1.3. Inflammation of the nasal mucosa in allergic rhinitis. Pollen-induced rhinitis is the most characteristic IgE-mediated allergic disease and is triggered by the interaction of mediators released by cells which are implicated in both allergic inflammation and nonspecific hyperreactivity (777). This disease can be mimicked by nasal challenge with pollen allergens (778) but such a challenge differs from the natural course of the disease in that it is a single provocation and does not reflect the multiple triggers which occur during the pollen season. It does not take into account the priming effect on the nasal mucosa which appears to play an important role in allergic rhinitis (72, 779).

Studies of cells infiltrating the nasal mucosa during the pollen season show that there is an increase in the numbers of various inflammatory cells and that this is correlated with both the severity of symptoms (777, 780–782) and nasal nonspecific hyperreactivity (783, 784). Eosinophils are almost always found in the mucosa between nondesquamated epithelial cells, in the submucosa and in nasal secretions (780, 785). Mast cells are present in increased numbers in the epithelium and the submucosa but they are often degranulated (785–788). $CD4^+$ T-cells are increased in number during the pollen season (789). Moreover, in allergic patients, there is an increase in Langerhan-like cells ($CD1^+$) during the season (790).

In patients with indoor allergy, nasal eosinophilia is not a permanent feature (78, 199, 791–793). Mast cells are not always increased in the mucosa.

The concept of 'minimal PER inflammation' is important (64, 78, 79). In patients with allergic rhinitis, the allergen exposure varies throughout the year and there are periods in which there is little exposure. This is the case in the Mediterranean area for HDMs during the summer, or when allergen avoidance is effective. However, these patients, even though they are symptom-free, still suffer inflammation of the nose.

Allergic rhinitis is characterized by an inflammatory infiltrate and the release of mediators responsible for the symptoms. Moreover, neurogenic mechanisms including a naso-nasal reflex play a role which is still not fully appreciated.

4.1.4. Inflammatory cells. The inflammatory infiltrate is made up of different cells.

Mast cells are not only effector cells of the immediate-phase response, but also play a role in ongoing allergic inflammation (795).

Eosinophils may differentiate from progenitors in the nasal mucosa during the pollen season (796). They are increased in numbers and activated in the nasal mucosa of symptomatic allergic patients (797).

T-cells, macrophages, fibroblasts and other cells participate in the inflammatory infiltrate of the nasal mucosa of patients with allergic rhinitis.

This cellular response includes:

- chemotaxis, selective recruitment and trans-endothelial migration of cells in particular by CC3 chemokines (798);
- localization of cells within the different compartments of the nasal mucosa. Mast cells are not only the effector cells of immediate-phase allergic reaction;
- activation and differentiation of various cell types;
- as well as a prolongation of their survival;
- release of mediators by these activated cells;
- regulation of local and systemic IgE synthesis and
- communication with the immune system and the bone marrow.

4.1.5. Mediators. A range of mediators are released in nasal secretions during the pollen season (799). These include CysLT (800, 801), ECP (802) and, inconstantly, histamine.

Histamine was discovered just after the turn of the century and rapidly became known as the mediator of allergic and anaphylactic reactions. In the late 1930s, it appeared that other chemical mediators such as the slow-reacting substances of anaphylaxis (SRS-A, now identified as CysLT) were involved in the allergic reaction. The mechanisms of the allergic reaction are now becoming better understood and although histamine (released by mast cells and basophils) is still one of the major effectors of the allergic reaction, many other mediators produced by different cell types are involved. Thus, mediators, cytokines, chemokines, neuropeptides, adhesion molecules and cells all cooperate in a complex network provoking the specific symptoms and the nonspecific hyperreactivity of allergic rhinitis.

Cysteinyl leukotrienes are a family of inflammatory lipid mediators synthesized from arachidonic acid by a variety of cells, including mast cells, eosinophils, basophils and macrophages, which play a role as multifunctional mediators in allergic rhinitis (803). Besides their vasoactive properties, CysLT are involved in the maturation, as well as in the tissue recruitment, of inflammatory cells.

4.1.6. Neurogenic mediators. The nose provides defensive and homeostatic functions requiring rapid responses to physical and chemical stimuli (804). As a result, it is armed with a complex nervous system that includes sensory, parasympathetic and sympathetic nerves. Sensory nerves transmit signals from the mucosa generating sensations such as pruritus, motor reflexes such as sneezing, and parasympathetic and sympathetic reflexes that affect the glandular and vascular nasal apparatuses

(805). Reflexes directed to the nose are also generated by inputs from other body regions. Hence, all symptoms that constitute the nosologic entity of rhinitis can be triggered through neural pathways. Neural function can be chronically upregulated in the presence of mucosal inflammation. The molecular mechanisms of hyperresponsiveness are not understood, but several inflammatory products appear to play a role. Neurotrophins, such as the nerve growth factor (806), are prime candidates as mediators of neural hyperresponsiveness (807).

4.1.7. Remodeling processes. In allergic rhinitis, remodeling is still poorly understood (19, 808, 809). Even though inflammation is similar in allergic rhinitis and asthma, the pathologic extent of nasal remodeling as well as its clinical consequences may be different from those of the bronchi.

Epithelial damage is only minimal in the nasal mucosa of patients with allergic rhinitis (810–812). Moreover, epithelial cell metaplasia has been observed in the nasal biopsies of some patients suffering from perennial rhinitis (813, 814). Although the nasal and bronchial mucosa are exposed to the same noxious environment (and even more so the nose), epithelial shedding is more pronounced in the bronchi than in the nose of the same patients suffering from asthma and rhinitis (19, 815).

The reticular basement membrane does not appear to be largely pseudo-thickened (815) although some collagen and fibrous protein deposition can be found on the reticular layer (816, 817). Moreover, the demonstration of fibrogenic growth factors in the nasal mucosa of patients with allergic rhinitis is unclear due to the paucity of studies (818, 819).

Matrix metalloproteinases are major proteolytic enzymes that are involved in extracellular matrix (ECM) turnover (820) but their role in allergic rhinitis is not fully understood (821, 822).

The stereological estimation of blood vessel surface and volume densities was studied in human normal and rhinitic nasal mucosa (823). The volume and surface densities of the cavernous blood vessels in rhinitis were unaltered and there was no evidence of vascular remodeling. On the other hand, the hypervascularity and overexpression of the platelet-derived endothelial cell growth factor and Vascular Endothelial Growth Factor (VEGF), an angiogenic factor, were found in allergic nasal mucosa (824, 825).

The epithelial–mesenchymal trophic unit (826) is of cardinal importance in asthma but this concept has reduced the importance of the smooth muscle as an inflammatory and regulatory cell (827). It is however possible that some of the differences in remodeling between the nasal and the bronchial mucosa are related to the smooth muscle cells interacting with the epithelium and other mesenchymal cells (827–829).

Many of the genes involved in IgE synthesis and airways (re)modeling might be conserved fetal genes (830) which may not have been silenced during early infancy. Their gene products might play an important role in the induction and maintenance of the pathogenesis of asthma (831). Since the nose and bronchi have a different embryologic origin, it might be proposed that the persistence of fetal genes is involved in the differences observed between the remodeling of the nose and the bronchi (19).

4.2. Nasal hyperreactivity and nonspecific triggers

Nonspecific nasal hyperreactivity is an important feature of allergic and nonallergic rhinitis (832) and can be defined as an increased nasal response to a normal stimulus resulting in sneezing, nasal congestion and secretion, either one of these symptoms or in various combinations.

This phenomenon can be observed after nasal stimulation (833) such as:

- heating of the nasal mucosa (834);
- challenge of the nose with cold air which can induce an inflammatory response with the activation of mast cells (835, 836) and the occurrence of a late-phase reaction (837);
- challenge of the nose with histamine (156, 838) or methacholine (839);
- acrolein (840);
- capsaicin (841);
- strong odors (842);
- distilled water (843);
- change of posture (844);
- change of body temperature (833) and
- consumption of hot drinks (soup; 845).

5. Burden

Burden of allergic rhinitis

- Allergic rhinitis is a global health problem that causes major illness and disability worldwide.
- Patients from all countries, all ethnic groups, all socioeconomic conditions and of all ages suffer from allergic rhinitis.
- In many countries, the prevalence of allergic sensitization is often higher than 50% of the population in some age groups.
- Using a conservative estimate, allergic rhinitis occurs in over 500 million people around the world.
- Allergic rhinitis is increasing in prevalence in areas with low or medium levels of prevalence. It may be plateauing or even decreasing in high prevalence areas.
- Allergic rhinitis affects social life, sleep, school and work.
- The economic impact of allergic rhinitis is often underestimated because direct costs for the disease are not elevated. The indirect costs are substantial.

5.1. Prevalence of allergic rhinitis

Despite recognition that allergic rhinitis is a global health problem and is increasing in prevalence (846–850), there are insufficient epidemiologic data using allergy tests, and more data are needed with regard to its etiologic risk factors and natural history. Many national or multinational studies are rapidly improving our knowledge in the prevalence of rhinitis and its possible risk factors. These include:

- the second National Health and Nutrition Examination Survey (275, 285);
- the ECRHS (851);
- the International Study on Asthma and Allergy in Childhood (ISAAC I; 852) and its follow-up study (ISAAC III; 853);
- the SAPALDIA (854) and
- the Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen (SCARPOL; 855).

The prevalence of an IgE sensitization to aeroallergens measured by allergen-specific IgE in serum or skin tests is over 40–50% in the population of Europe, the USA and Australia–New Zealand (68, 856–859). Most but not all sensitized subjects suffer from allergic rhinitis and/or asthma.

The clinical definition of rhinitis is difficult to use in the epidemiologic settings of large populations where it is impossible to visit everybody individually or to obtain the laboratory evidence of each immune response. It seems that there is an overestimation of allergic rhinitis using questionnaires only (854, 860) and that the attributable fraction of IgE-mediated allergy in patients with a diagnosis of allergic rhinitis by questionnaires is slightly over 50% (47). Thus, studies using questionnaires only may overestimate the true prevalence of allergic rhinitis. On the other hand, many subjects suffer from nonallergic rhinitis. Nonallergic rhinitis was reported to account for 30–70% of patients with chronic perennial rhinitis (82, 861).

5.1.1. Monocentric studies. Most epidemiologic data concern seasonal allergic rhinitis, but not exclusively. The prevalence of seasonal allergic rhinitis using questionnaires ranges from 1% to 40% (Table 8) The prevalence of perennial rhinitis varies from 1% to 13%.

Table 8. Cumulative prevalence of allergic rhinitis in monocentric epidemiologic surveys

Country	Year	Author	Reference	*N*	Age group (years)	Seasonal rhinitis (%)	Perennial rhinitis (%)	Nasal symptoms or AR (%)
Australia	1997	Downs	862	1282	7–12	nonaborigines 44.2		
				158	7–12	Aborigines 31.4		
Canada	1999	Lévesque	863	1520	9	9.7		16.98
China	2002	Yu	648	11 580	7–15			27.6
				2621				21.8
Denmark	1995	Mortz	864	1606	12–16	12.5	9.0	15.7
Finland	*1992*	Varjonen	865	1712	15–16	14		
France	1991	Harf	866	629	Adult	18.5		
	1992	Vervloet	54	2067	20–60	5.9		
	1995	Pariente	52	35 615	>18		4.1	
Finland	1979	Alanko	867		10–19	2.7 (rural)		
	1979	Haahtela	868		15–17	22		
	1992	Varjonen	865		15–16	14		
Germany	1992	Dold	869	3984	9–11	9.5		
	1994	Weiland	694	2050	13–16	22.5		
The Netherlands	1996	Droste	55	2167	20–70	6.6	12.7	29.5
Israel	1998	Kivity	277	658	8–17			Arabs: 9.7
Italy	1997	Matricardi	870	1649	Men	13.3		
	1998	Astarita	871	1998	9–15	13.1		
Japan	1990	Ogino	872	471	18–22	32.7		
	1994	Okuma	873	1013	6–15	12.9		
	1992	Okano	874	431	School			22.5
	1995	Sakurai	848	2307	M: 19–65			34.5
	1996	Suguru	875	15 234	6–9			15
Korea	1997	Min	876	9069	All		1.14	
Norway	1990	Bakke	877	4492	15–70	10.0		
	1994	Dotterud	878	551	7–12	20.6		
Poland	1995	Breborowski	879		6–15	16.7		
Russia	1994	Dotterud	880	1684	8–17			13.9

Table 8. Continued

Country	Year	Author	Reference	*N*	Age group (years)	Seasonal rhinitis (%)	Perennial rhinitis (%)	Nasal symptoms or AR (%)
Scotland	1998	Hannaford	881	7244	>14	18.2		
Singapore	*1994*	Ng	882	2868	20–74	4.5		
	1996	Goh	883	6238	6–7			13.4
	2000	Wang	48	4602	6–80			Persistent rhinitis: 13.1
Spain	1999	Azpiri	884	2216	10–40	10.6		
Sweden	1990	Hattewig	885	1654	7		8	
	1992	Brattmo	725	511	18			39
	1997	Olsson	727	10 670	19–80	24		
	1987	Norrman	886	1112	13–18	17		
	1995	Aberg	887	2481	7	13		
Switzerland	1926	Rehsteiner	888				0.28	
	1984	Varonier	888	4781	5–6	0.5	0.6	
	1995	Wuttrich	854	8357	16–60	14.2		
Taiwan	*2003*	Chen	294	1472	6–8			39.8
Thailand	1994	Bunnag	889	3124	11 to >50			13.15
Turkey	1997	Kalyoncu	890	738	6–13			18.7
	1997	Ozdemir	891	1603	Students			9.7*
	2006	Unlu	892	1366	13–18			8.1
	2002	Tomac	893	1500	6–9			37.7
	2002	Dinmezel	894	995				27.7
UK	1989	Howarth	895	1792	16–20	18		
	1989	Burr	896	965	12	14.9		
	1986	Sibbald	33	2969	16–65	3	13.2	24
	1992	Ninan	897	1989	8–13	11.9		
	1992	Richards	46	813	5–59	29		
	1995	Strachan	898	12 355	23	16.5		
	1998	Jones	899	2114	>14	18.9	8.6	
	1999	Arshad	860	1456	10			22.6
USA	1969	Hagy	900	1836	16–21	21.1	5.2	
	1974	Broder	901	9226	4–7	10.2		
	1988	Turkeltaub	275	12 742				20.4
	1994	Wright	721	747	9	42		

N, number of subjects.
* Only 28% of rhinitis patients had positive skin prick tests.

In a survey, skin prick testing with eight nonstandardized extracts of inhalant allergens confirmed that perennial rhinitis was often associated with allergy as there was an excess of skin prick test positivity to cat or dog among individuals suffering from perennial rhinitis (275, 285).

In the Tucson study, it was found that 42% of children had doctor-diagnosed rhinitis at 6 years of age (721).

The prevalence of seasonal allergic rhinitis is higher in children and adolescents than in adults. Perennial rhinitis is more common in adults than in children but few reliable data exist (861).

In many parts of the world, pollen allergy is very common, but in Eastern Asia, Latin America and tropical areas, mite allergy is more common.

In more recent studies, the prevalence of allergic rhinitis has increased, in particular in countries with low prevalence (636, 902–909).

5.1.2. Studies using the ARIA definition. In a study on the general population in Europe, the prevalence of allergic rhinitis was found to be around 25% (62, 63). The prevalence of confirmable allergic rhinitis in adults in Europe ranged from 17% (Italy) to 28.5% (Belgium; Table 9).

Table 9. Prevalence of allergic rhinitis in the general population [from Refs (62, 63)]

			Self-reported (%)		Type (%)	
	Age (years)	Prevalence of allergic rhinitis (%)	Self-aware	Doctor diagnosed	Persistent	Intermittent
Belgium	39.0	28.5	65.3	52.5	24.8	72.0
France	38.8	24.5	60.6	45.7	28.7	55.4
Germany	38.0	20.6	83.0	66.0	41.7	19.2
Italy	41.5	16.9	83.8	70.3	32.4	35.1
Spain	31.3	21.5	64.0	52.0	21.0	48.5
UK	42.7	26.0	80.8	57.7	53.8	57.7

5.1.3. SAPALDIA. The Swiss Study on Air Pollution and Lung Diseases in Adults, a cross-sectional study of 9 651 adults carried out in 1991–1993, studied the prevalence of bronchial asthma, chronic bronchitis and allergic conditions in the adult population of Switzerland and examined the risk factors for these diseases, particularly air pollution (910–912) and allergy.

On the basis of a positive Phadiatop® and/or a positive skin prick test to common aeroallergens, 32.3% of the study population was considered atopic (males 35.7%, females 28.8%). The highest rate of positive skin prick tests was observed for grass pollen (12.7%), followed by HDM (8.9%), birch (7.9%), cat (3.8%) and dog (2.8%) (56, 854).

The prevalence of allergic rhinitis (rhinitis symptoms associated with atopy) was 13.5% (males 14.3%, females 12.6%).

The prevalence of current seasonal allergic rhinitis varied between 9.1% (questionnaire answer and a positive skin prick test to at least one pollen), 11.2% (questionnaire answer and presence of atopy) and 14.2% (questionnaire answer only).

5.1.4. SCARPOL. The impact of long-term exposure to air pollution on respiratory and allergic symptoms and illnesses was assessed in a cross-sectional study of school children (aged from 6 to 15 y, $N = 4\,470$) in Switzerland (284, 913). Sensitization to any allergen was most strongly associated with reported seasonal allergic rhinitis (OR = 5.7), nose problems accompanied by itchy-watery eyes (OR = 4.4), symptoms occurring only during the pollen season (March through September; OR = 4.9) and a combination of these latter two symptoms (OR = 5.8). Finally, the underdiagnosis of allergic rhinitis was found to be common. Children growing up on a farm were less likely to be sensitized to common aeroallergens and to suffer from allergic diseases than children living in the same villages but in nonfarming families (855).

5.1.5. ISAAC. The ISAAC was founded to maximize the value of epidemiologic research on asthma and allergic disease, by establishing a standardized methodology and facilitating international collaboration. Its specific aims are (914):

- to describe the prevalence and severity of asthma, rhinitis and eczema in children living in different centers, and to make comparisons within and between countries;
- to obtain baseline measures for the assessment of future trends in the prevalence and severity of these diseases and
- to provide a framework for further etiologic research into genetic, lifestyle, environmental and medical-care factors affecting these diseases.

The ISAAC design comprises three phases (915):

- Phase I used core questionnaires designed to assess the prevalence and severity of asthma and allergic disease for two age groups. It was completed in 156 collaborating centers in 56 countries: 463 801 children in the 13- to 14-y age group and 257 800 in the 6- to 7-y age group. One of the problems raised with this study was that only a questionnaire was used and that responses for rhinitis may overestimate the real prevalence of the disease (284). Moreover, there was a season-of-response effect on the responses to the questions on rhinitis symptoms suggesting a recall bias relating to recent symptoms (916);
- Phase II investigated possible etiologic factors, particularly those suggested by the findings of Phase I and
- Phase III was a repetition of Phase I to assess trends in prevalence (853).

The International Study on Asthma and Allergy in Childhood Phase I has demonstrated a large variation in the prevalence of asthma and rhinitis symptoms in children throughout the world. The prevalence of rhinitis with itchy-watery eyes ('rhinoconjunctivitis') over the past year varied across centers from 0.8% to 14.9% in 6–7-year olds and from 1.4% to 39.7% in 13–14-year olds (697, 852, 883, 917–937). The overall correlation between the prevalence of asthma and rhinitis in school children was significant (852, 917). In particular it was found that countries with a very low prevalence of asthma ($< 5\%$) such as Indonesia, Albania, Romania, Georgia and Greece also had low prevalences of rhinitis. On the other hand, the countries with a very high prevalence of asthma ($> 30\%$) such as Australia, New Zealand and the United Kingdom had a high prevalence of rhinitis (15–20%). Other countries with a very high prevalence of rhinitis [Nigeria ($> 35\%$), Paraguay (30–35%), Malta, Argentina, Hong Kong (25–30%), Brazil (7–25% in different centers)] had asthma prevalences ranging from 10% to 25%. It is likely that environmental factors were responsible for the major differences between countries.

The results of ISAAC Phase III have been published (853; Table 10).

Table 10. Prevalence of asthma and rhinitis in the ISAAC Phase III study [from Asher et al. (853)]

		Asthma symptoms			Allergic rhinoconjunctivitis symptoms			Eczema symptoms		
	Years between phases	Phase 1	Phase 3	Change per year	Phase 1	Phase 3	Change per year	Phase 1	Phase 3	Change per year
6- to 7-year age group										
Africa (English speaking)										
Nigeria	7.0	4.8	5.6	0.10	3.7	3.6	−0.01	4.5	5.0	0.07
Asia-Pacific										
Hong Kong	6.0	9.1	9.4	0.03	13.7	17.7	0.67	3.9	4.6	0.12
Indonesia	6.0	4.1	2.8	−0.21	3.8	3.6	−0.03	–	–	–
Japan	8.0	17.4	18.2	0.10	7.8	10.6	0.35	–	–	–
Malaysia (3)	6.3	6.5	5.8	−0.12	4.1	4.8	0.11	9.5	12.6	0.49
Singapore	7.0	15.7	10.2	−0.80	8.5	8.7	0.02	2.8	8.9	0.87
South Korea (2)	5.0	13.3	5.8	−1.45	9.8	8.7	−0.18	8.8	11.3	0.52
Taiwan	7.0	9.6	9.8	0.04	14.6	24.2	1.37	3.5	6.7	0.46
Thailand (2)	6.0	8.2	11.9	0.47	7.3	10.4	0.30	11.9	16.7	0.79
Eastern Mediterranean										
Iran (2)	6.0	5.4	12.0	1.14	1.5	2.2	0.12	1.1	2.0	0.13
Malta	7.0	8.8	14.9	0.86	7.2	8.9	0.24	4.2	4.0	−0.03
Sultanate of Oman	6.0	7.1	8.4	0.21	6.2	7.0	0.13	4.2	4.2	0.00
Indian subcontinent										
India (6)	7.5	6.2	6.8	0.06	3.2	3.9	0.05	3.0	2.4	0.00
Latin America										
Brazil	7.0	21.3	24.4	0.44	12.5	12.0	−0.07	6.8	6.8	0.00
Chile (3)	7.0	18.2	17.9	−0.06	8.2	12.3	0.56	10.9	12.9	0.26
Costa Rica	8.0	32.1	37.6	0.69	11.6	15.9	0.54	8.7	8.9	0.02
Mexico	8.0	8.6	8.4	−0.03	8.6	7.2	−0.17	4.9	4.0	−0.11
Panama	6.0	23.5	22.7	−0.13	7.1	11.7	0.77	7.9	14.4	1.09
North America										
Barbados	6.0	18.9	19.5	0.11	5.5	6.4	0.15	6.7	9.2	0.42
Canada	9.0	14.1	18.2	0.47	8.2	10.8	0.29	8.7	12.0	0.36
Northern and Eastern Europe										
Albania	5.0	7.6	5.0	−0.53	4.1	3.9	−0.03	2.5	3.7	0.24
Estonia	7.0	9.3	9.6	0.05	3.5	4.2	0.11	9.8	11.5	0.24
Georgia	7.0	9.3	6.9	−0.34	3.9	2.8	−0.16	5.1	2.4	−0.39
Lithuania	7.0	4.6	6.6	0.28	3.2	3.8	0.08	2.3	3.0	0.09
Poland (2)	7.0	10.9	13.6	0.38	7.2	13.0	0.78	6.3	11.5	0.77
Russia	6.0	11.1	11.4	0.05	5.6	4.7	−0.16	9.4	6.6	−0.46
Sweden	8.0	10.3	10.2	−0.01	8.0	6.9	−0.14	19.5	22.3	0.35
Ukraine	4.0	12.2	12.5	0.07	9.7	7.7	−0.51	6.2	5.3	−0.21
Oceania										
Australia	9.0	27.2	20.0	−0.80	9.8	12.9	0.34	11.1	17.1	0.67
New Zealand (4)	9.5	23.6	22.2	−0.11	9.5	11.4	0.19	14.3	15.0	0.08
Western Europe										
Austria (2)	7.0	7.8	7.4	−0.05	5.1	6.1	0.15	5.7	6.1	0.05
Belgium	7.0	7.3	7.5	0.02	4.9	5.8	0.13	7.7	11.6	0.56
Germany	5.0	9.6	12.8	0.65	5.4	6.9	0.30	6.7	7.9	0.23
Italy (6)	8.0	7.5	7.9	0.07	5.4	6.5	0.15	5.8	10.1	0.53
Portugal (3)	7.0	13.2	12.9	−0.07	8.7	9.3	0.16	9.6	9.7	0.09
Spain (6)	7.3	6.2	9.5	0.44	5.4	7.9	0.33	3.4	5.9	0.31
UK	5.0	18.4	20.9	0.50	9.8	10.1	0.05	13.0	16.0	0.60
13- to 14-year age group										
Africa (English speaking)										
Ethiopia	8.0	10.7	9.1	−0.20	10.6	9.9	−0.09	19.9	19.0	−0.12
Kenya (2)	6.0	13.9	15.8	0.35	14.2	21.2	0.94	10.4	15.2	0.83
Nigeria	6.0	10.7	13.0	0.38	39.7	16.4	−3.88	17.7	7.7	−1.66
South Africa	7.0	16.1	20.3	0.60	15.1	20.7	0.80	8.3	13.3	0.71
Africa (French speaking)										
Algeria	6.0	5.9	8.7	0.48	9.9	20.7	1.80	3.2	6.5	0.56
Morocco (2)	6.5	7.8	10.4	0.00	13.1	21.6	1.12	10.7	21.8	1.72
Tunisia	5.0	8.5	11.9	0.67	35.8	23.2	−2.52	8.0	9.4	0.28

Table 10. Continued

		Asthma symptoms			Allergic rhinoconjunctivitis symptoms			Eczema symptoms		
	Years between phases	Phase 1	Phase 3	Change per year	Phase 1	Phase 3	Change per year	Phase 1	Phase 3	Change per year
Asia-Pacific										
China (2)	7.0	4.3	6.0	0.24	8.1	10.4	0.33	1.2	1.4	0.05
Hong Kong	7.0	12.4	8.6	−0.55	24.0	22.6	−0.21	2.7	3.3	0.08
Indonesia	6.0	2.1	5.2	0.52	5.3	4.8	−0.08	1.2	2.2	0.16
Japan	8.0	13.4	13.0	−0.05	14.9	17.6	0.34			
Malaysia (3)	6.3	10.1	8.9	−0.13	13.9	16.2	0.53	8.9	9.9	0.19
Philippines	7.0	12.3	8.4	−0.55	15.3	11.0	−0.61	5.2	7.8	0.37
Singapore	7.0	9.8	11.4	0.24	15.1	16.5	0.20	7.4	9.2	0.25
South Korea (2)	5.0	7.7	8.7	0.20	10.2	11.6	0.28	3.8	5.7	0.39
Taiwan	6.0	5.4	7.0	0.26	11.7	17.8	1.02	1.4	4.1	0.45
Thailand (2)	6.0	13.1	11.6	−0.21	15.5	21.0	0.84	8.2	9.6	0.39
Eastern Mediterranean										
Iran (2)	6.5	10.9	13.2	0.17	7.5	9.8	0.31	2.6	4.4	0.30
Kuwait	6.0	17.1	7.6	−1.59	12.6	10.7	−0.32	8.4	6.1	−0.38
Malta	7.0	16.0	14.6	−0.20	29.0	20.9	−1.15	7.7	5.4	−0.33
Pakistan	6.0	8.5	11.7	0.53	18.1	16.8	−0.22	9.6	13.2	0.61
Sultanate of Oman	6.0	8.9	8.4	−0.08	11.4	15.2	0.63	4.7	7.1	0.39
Indian subcontinent										
India (8)	7.1	6.7	6.4	0.02	6.3	10.0	0.43	4.3	3.7	−0.03
Latin America										
Argentina	5.0	11.2	13.6	0.48	17.4	16.9	−0.09	7.4	6.3	−0.23
Brazil (5)	7.4	22.7	19.9	−0.42	16.2	15.8	−0.05	5.3	4.2	−0.08
Chile (3)	6.7	10.2	15.5	0.84	10.7	22.2	1.12	9.6	16.1	0.86
Costa Rica	8.0	23.7	27.3	0.46	14.3	17.7	0.43	7.2	6.3	−0.11
Mexico	8.0	6.6	11.6	0.63	9.4	7.1	−0.28	4.4	2.8	−0.20
Panama	6.0	17.6	22.9	0.88	9.4	11.7	0.40	7.8	14.5	1.11
Paraguay	5.0	19.4	20.9	0.31	34.5	45.1	2.12	10.8	17.7	1.38
Peru	6.0	26.0	19.6	−1.06	19.4	18.7	−0.12	8.2	10.5	0.38
Uruguay	8.0	19.0	17.9	−0.13	16.0	10.6	−0.67	7.2	5.2	−0.25
North America										
Barbados	5.0	17.7	20.8	0.62	11.0	11.8	0.16	5.0	7.0	0.40
USA	8.0	22.9	22.3	−0.07	13.4	19.1	0.71	8.5	8.3	−0.03
Northern and Eastern Europe										
Albania	6.0	2.6	3.4	0.12	4.0	5.5	0.24	0.8	2.0	0.19
Estonia	7.0	8.6	9.3	0.09	4.7	6.3	0.22	6.6	8.7	0.29
Finland	7.0	13.1	19.0	0.84	15.3	15.5	0.04	13.2	15.6	0.34
Georgia	7.0	3.6	5.1	0.21	4.5	4.5	−0.01	2.8	1.8	−0.14
Latvia	10.0	8.3	10.5	0.22	5.3	4.5	−0.08	5.2	3.4	−0.19
Lithuania	6.0	8.2	6.7	−0.24	5.6	4.6	−0.17	1.7	1.8	0.02
Poland (2)	7.0	7.8	10.2	0.35	8.8	18.9	1.35	5.0	8.5	0.44
Romania	7.0	3.0	22.7	2.81	5.2	14.3	1.29	6.3	5.4	−0.13
Russia	6.0	9.9	11.2	0.22	7.8	11.7	0.65	4.9	3.8	−0.18
Sweden	8.0	12.6	9.7	−0.36	11.1	10.4	−0.09	15.8	12.9	−0.37
Ukraine	4.0	12.9	20.9	2.01	11.2	11.2	−0.01	5.3	5.7	0.11
Oceania										
New Zealand (5)	9.0	29.7	26.7	−0.39	19.1	18.0	−0.13	12.9	8.8	−0.44
Western Europe										
Austria	8.0	11.8	15.1	0.41	9.2	9.7	0.06	5.3	7.5	0.28
Belgium	7.0	12.0	8.3	−0.52	14.5	16.9	0.34	6.7	7.2	0.07
Channel Islands (2)	5.5	35.1	26.5	−1.62	17.3	15.0	−0.45	17.0	11.0	−1.04
Germany	5.0	14.2	17.5	0.68	14.4	15.0	0.12	7.1	7.7	0.12
Isle of Man	6.0	33.4	31.2	−0.36	20.1	20.2	0.02	15.6	11.1	−0.76
Italy (9)	7.9	9.4	8.4	−0.22	14.3	15.5	0.07	6.2	7.7	0.16
Portugal (4)	7.8	9.5	12.0	0.32	7.0	9.5	0.40	4.4	5.1	0.16
Republic of Ireland	8.0	29.1	26.7	−0.30	19.3	15.5	−0.48	13.6	8.6	−0.62
Spain (8)	7.6	9.3	9.6	0.04	13.9	15.0	0.10	4.1	4.0	−0.01
UK (6)	7.3	31.0	24.7	−0.71	18.9	15.3	−0.57	14.7	10.6	−0.39

5.1.6. ECRHS. The ECRHS was set up to answer specific questions about the distribution of asthma and the health care given for asthma in the European Community (45). Specifically, the survey was designed:

- to estimate variations in the prevalence of asthma, asthma-like symptoms and airway responsiveness;
- to estimate variations in exposures to known or suspected risk factors for asthma;
- to assess to what extent these variations explain the variations in the prevalence of the disease and
- to estimate differences in the use of medication for asthma.

No cooperative study on allergic rhinitis has been carried out among adults but the ECRHS has questioned 'nasal allergy' in comparable representative samples (45).

The protocol provides specific instructions on the sampling strategy adopted by the survey teams. It also provides instructions on the use of the questionnaires, the allergy tests, lung function measurements, tests of airway responsiveness as well as blood and urine collection.

Results for the prevalence of 'nasal allergy' have been published in only a few studies (55, 851, 938–941). The findings of Droste et al. (55) confirmed the close relationship of skin test positivity with reported symptoms of nasal allergy in a general population. Specific IgE positivity also shows a close relationship with nasal symptoms in response to allergen exposure in a general population. Skin testing and specific IgE measurement may be considered complementary to one another in the diagnosis of allergic rhinitis.

5.2. Variations in allergy prevalence

An increase in the prevalence of allergic rhinitis has been observed over the past 40 y of the last millennium (252, 721, 847, 897, 942–950). In a study in Australia with 50% aborigines, it was found that allergic rhinitis increased from 1982 to 1992 but not in 1997 (951). There are some signs of reversing trends (952), but more data are needed. These studies proposed different reasons for these trends which may be related to allergen load or co-factors.

In ISAAC III (853), it was found that in the 6- to 7-y age group, there is a global increase in rhinitis prevalence across most countries. In the 13- to 14-y age group, there is also a global increase in allergic rhinitis in countries where low, medium and high prevalence rates were found during ISAAC Phase I (Table 11). On the other hand, rates are plateauing or decreasing in countries with high prevalence.

Table 11. Variations in prevalence in allergic rhinitis in studies not included in ISAAC III

Country	Author	Reference	Year	Age (years)	SAR (%)	Nasal symptoms of AR (%)
Denmark	Linneberg	944	1989	15–41	22.3	
			1997	15–41	31.5	
Finland	Rimpela	953	1977–1979	12–18	5	
			1991	12–18	14.9	
	Latvala	954	1966	Military	0.5	
			1990	recruits	5.1	
			1997		8.2	
East Germany	Von Mutius	250	1991–1992	9–11		2.3
			1995–1996			5.1
Norway	Selnes	948	1985	School children	16.5	
			1995		24.7	
			2000		29.6	
Sweden	Aberg	846	1971	Army recruits	4.4	
	Aberg	943	1979		5.45	
	Aberg	846	1981	Army recruits	8.4	
	Aberg	943	1991		8.1	
	Braback	955	1952–1956	Military recruits		4.3
			1957–1961			6.0
			1962–1966			7.9
			1967–1971			12.2
			1972–1977			16.1
Switzerland	Varonier	888	1970	15	4.4	
			1980	15	4.4	
	Wuttrich	956	1885	15–24	16	
	Wuttrich	854	1991	18–60	14.2	
	Grize	957	1992	5–7	5.0	
			1995		5.6	
			1998		5.4	
			2001		4.6	

Table 11. Continued

Country	Author	Reference	Year	Age (years)	SAR (%)	Nasal symptoms of AR (%)
Thailand	Bunnag	889	1975	6–34		23. 6
			1995			21.9
Turkey	Demir	947	1993–1994	5–18		4.6
			2001–2002			13.6
UK	Butland	252	1974	16	12.0	
			1986		23.3	
	Upton*	723	1972–1976	45–54	5.0	
			1996	45–54	19.9	
	Ninan	897	1964	8–13	3.2	
			1989	8–13	11.9	
	Burr		1973	12	9	
			1988	12	15	

* Parents and offspring.

In countries where the prevalence of allergy and rhinitis is high, a reduction in increase, a plateau or a slight reduction have been observed. On the other hand, in countries with low prevalence, there is a considerable increase in allergy and rhinitis. Trends in asthma and rhinitis prevalence do not always accord.

5.2.1. Rural–urban differences and modification of lifestyle. Studies in North America (285), Europe (41, 958), Central America (959) and South Africa (960) have shown that the prevalence of atopy and allergic rhinitis is higher in urban than in rural areas (961). This is particularly the case for pollinosis, whereas pollen counts are usually higher in urban than in rural areas. Selection bias may act by selecting people who can live in the countryside (285, 854, 962–964), but confounding factors are likely to exist.

The children of farmers have less allergic rhinitis than other children, suggesting that a countryside lifestyle could possibly protect children from the development of allergy (855, 965–969). Most consistently, the 'protective' farm effect was related to livestock farming and thus to microbial exposure (753). A dose-dependent inverse relationship between the exposure to endotoxin in the mattress dust of children and the occurrence of atopic diseases was shown in rural environments in Europe (970, 971). Muramic acid, a constituent of peptidoglycan, is present in Gram-negative and Gram-positive bacteria in the environment, but is not an additional marker of microbial exposure (972). Another possible protective mechanism is the ingestion of nonpasteurized milk in infancy (973).

In 1989, in East German children, there was a reduced prevalence of atopy and seasonal allergic rhinitis by comparison to West German children (958, 974). Similar trends have been observed in the Baltic States and Scandinavia (975) or between Finland and Russia (976). Although there is some controversy (977, 978), it seems that the prevalence rate of atopy and seasonal allergic rhinitis is now similar in all parts of Germany (250). However, in some former Eastern European countries such as Estonia, the prevalence of allergy does not appear to increase due to a change in lifestyle (965, 979).

Asthma and allergic diseases in developing countries are associated with the adoption of an urbanized 'western' lifestyle (980–986). However, in rural areas, the prevalence of sensitization to aeroallergens such as HDMs determined by specific IgE is common but skin tests to these allergens are usually negative (987). Some studies suggest that in tropical areas, where parasites are endemic, the relationship between asthma and IgE is different from that of areas without major parasitic disease (987–990). Many nonexclusive reasons may explain that IgE-mediated hypersensitivity reactions are rare in patients with chronic helminth infections, even though basophils and mast cells in these patients are sensitized to antiparasite IgE and exposed to large amounts of parasite antigens. These include the production of IgG_4 'blocking antibodies' in the serum of the infected individual (991–994) and Th2 responses without atopy with elevations of anti-inflammatory cytokines, such as IL-10, that occur during long-term helminth infections and are inversely correlated with allergy (995–997). High degrees of parasite infection may prevent asthma symptoms in atopic individuals (998), and the long-term treatment of parasitic patients with antiparasitic drugs increases skin test reactivity to inhalant allergens (999).

5.2.2. Infections in the neonatal period and the hygiene hypothesis. Several studies have found an inverse relationship between atopy, seasonal allergic rhinitis (and asthma) and sib-ship size and order (252, 1000–1002). Seasonal allergic rhinitis is less frequent in large families even after taking the month of birth into account (42).

Strachan first proposed that infections and unhygienic contact might confer protection against the development of allergy (1000): the so-called hygiene hypothesis which may operate in allergic and autoimmune diseases (1003). Three major hypotheses have developed and explored the role of overt viral and bacterial infections, the significance of environmental exposure to microbial compounds and the effect of both on underlying responses of the innate and adaptive immunity. To date, a truly unifying concept has not yet emerged (1004) and there are some concerns about this hypothesis (1005).

An inverse association between tuberculin responses and atopy was observed in Japanese children (1006), indicating that BCG immunization, subclinical exposure to *Mycobacterium tuberculosis* without clinical disease, or host characteristics may influence the T-helper (Th) lymphocyte balance with decreased atopy as a result. However, no relationship between tuberculin reactivity and atopy in BCG-vaccinated young adults was found in developed (1007, 1008) and developing countries (1009, 1010). In developed countries, many studies found an absence of any relationship between BCG vaccination and atopic diseases in children (1011–1017) and young adults (1008). In other developing countries, there was a weak protective effect of BCG vaccination against asthma and hay fever (1018–1020). In developing countries, an early BCG vaccination was associated with a weak prevention of atopic diseases (1009). A *M. tuberculosis* infection may protect against allergy in a tuberculosis endemic area (1021, 1022).

Childhood immunization against infectious diseases [diphtheria-tetanus-pertussis (DTP)] or Measles-Mumps-Rubella (MMR) may protect from the development of atopic disease or inversely may increase it (1023), but the relationships are complex and no definite conclusion can be raised (1024). However, the benefit of vaccination is such that the potential and unproven risk of increased allergic disorders should not be considered.

Infectious diseases such as hepatitis or salmonellosis can be inversely associated with allergy (870, 1025, 1026).

Priming of the immune responses against allergens takes place *in utero*. In addition, early-life events are essential in shaping the immune answer towards the Th1 or Th2 profile, associated with a nonallergic or allergic phenotype, respectively. The hygiene hypothesis suggests that an early-life environment primes the immune system in the Th1 direction (nonallergic) while a 'sterile' environment tends to promote the development of allergy. The current view of cellular and molecular mechanisms underlying these phenomena includes fine balancing between innate immune mechanisms and Th1, Th2 and regulatory T-cells (1027, 1028).

Several questions remain unresolved, concerning notably the nature of protective infections, the mechanisms of protection, the spectrum of diseases concerned by the hypothesis, the difference between triggering and protective infections and finally the strategies which could be devised to mimic the effect of infections (1003). Moreover, the hygiene hypothesis differs in countries where helminth infections are common (995, 996) and atopy might prevent against enteric infections (1029).

5.2.3. Other factors

- Changes in lifestyle (915). An anthroposophic lifestyle, such as a restrictive use of antibiotics and vaccinations and a diet containing live lactobacilli, appears to prevent the development of allergy in Sweden (1023).
- Obesity may increase the prevalence or the severity of symptoms in patients with allergic rhinitis, but more data are needed (1030–1032).
- Increase in exposure to allergen (1033), pollution (748) and irritants (smoke, gas...; 711, 1034). Studies on the relationship between allergy in parents and allergy in their offspring should always consider the home environment as a potential confounder. For allergy prevention, results imply that among allergic parents there is an awareness and willingness to take measures to reduce exposure to indoor allergens (1035).
- Modification of diet responsible for the diminution of the intake of protective nutrients (1036, 1037).
- The link between physical activity, allergic diseases and asthma needs to be investigated in more detail (1005, 1038).
- Stress.

5.2.4. Natural history. Most longitudinal studies have explored the development of asthma in individuals suffering from allergic rhinitis. In many patients, rhinitis is an independent risk factor for the development of asthma (see Chapter 9).

The prognosis of allergic rhinitis classically depends on age and sex but no clear data are available. With age, rhinitis symptoms tend to become milder (252, 275, 721) and simultaneously the allergic skin reactivity decreases in the elderly (1039). Some studies found an increased prevalence of allergic rhinitis in young adults (1040–1046).

A few studies have examined the incidence and remission of allergic rhinitis in the same general population. A study from Denmark showed that the remission of allergic rhinitis symptoms was relatively infrequent, and that the remission of both symptoms and IgE sensitization was rare (1047). A study in Sweden (1048) showed that the prevalence of allergic rhinitis increased from 12.4% in 1992 to 15.0% in 2000. The incidence of allergic rhinitis from 1992 to 2000 was 4.8%, while 23.1% of the cases with allergic rhinitis in 1992 stated no rhinitis symptoms in 2000 indicating remission. After a 10-y course of the disease, 20% of patients with nonallergic rhinitis reported spontaneous disappearance and 36% improvement (861).

The 'Allergy March' from birth to adolescence is important in the understanding of the development of allergic rhinitis and other diseases (see Chapters 9 and 11.1). In birth cohorts, it was found that the development of pollen-induced allergic rhinitis is characterized by a marked increase in prevalence and incidence after the second year of life (1049). This study indicates that in combination with the risk of allergic predisposition, at least two seasons of pollen allergen exposure are needed before allergic rhinitis becomes clinically manifest.

5.2.5. Conclusion. Asthma and allergic rhinitis are common health problems that cause major illness and disability worldwide. Studies such as the ISAAC (917) and the ECRHS (45) have demonstrated that asthma is a prevalent condition in most countries. These studies suggest that there are more than 300 million people worldwide who are affected by asthma (1050). Rhinitis is similarly seen as a worldwide condition with lifetime prevalence estimates of between 10% and 20% of the population in the USA, UK, Germany, Switzerland and Finland (854, 953, 1051, 1052).

Using a conservative estimate, it is proposed that allergic rhinitis occurs in approximately 500 million people.

- Over 100 million people in Europe and North America.
- Over 150 million in Asia-Pacific.
- Over 100 million in India, Pakistan and surrounding countries.
- Over 75 million in Central and South America.
- Over 30 million in Africa.
- Over 50 million in other countries.

About 200 million people also have asthma as a co-morbidity. Moreover, nonallergic rhinitis/rhinosinusitis occurs in hundreds of millions of people around the world with the fraction attribute to allergy in studies using a rhinitis questionnaire being around 50–60%, but the estimation is currently difficult.

Allergic rhinitis is a very common disease in western lifestyle countries. It tends to be more common in developed countries. Furthermore, an increase in the prevalence of allergic rhinitis is commonly observed in developing countries. However, knowledge of allergic rhinitis is far from complete. More studies on the epidemiology of allergic rhinitis should be advocated. They may provide useful clues towards the interpretation of the immunological abnormalities associated with allergic diseases in general.

5.3. Social life

It is now recognized that allergic rhinitis comprises more than the classical symptoms of sneezing, rhinorrhoea and nasal obstruction. It is associated with impairments in how patients function in day-to-day life (1053). It has been known for a long time that having an allergic reaction causes significant fatigue and mood changes (1054), some impairment of cognitive function (1055, 1056), depression and anxiety (1057, 1058). Impairments on QOL and work and school performance are common, particularly in patients with moderate/severe symptoms.

Quality of life is a concept including a large set of physical and psychological characteristics assessing problems in the social context of the lifestyle. In rhinitis, two types of health-related quality of life (HRQOL) measures – generic and specific – have been used (1059–1061).

5.3.1. Generic QOL questionnaires. Generic questionnaires measure physical, mental and psychosocial functions in all health conditions irrespective of the underlying disease and can be used in the general population. The advantage of generic instruments is that the burden of illness across different disorders and patient populations can be compared.

Generic questionnaires include the Sickness Impact Profile, the Nottingham Health Profile and the Medical Outcomes Survey Short-Form 36 (SF-36; 1062). The SF-36 has been used to characterize patients with perennial rhinitis (52, 88), seasonal (1063–1065) and PER (1066–1068). A new instrument examining satisfaction in 32 aspects of daily life [the Satisfaction Profile (SAT-P)] was used in seasonal allergic rhinitis and was found to correlate with the SF-36 data (1069).

Rhinitis-related HRQOL appears to be moderately correlated with the more classical outcome variables used in clinical trials such as daily symptom scores (1069) and nasal hyperreactivity (1070). These observations are in line with the results of studies comparing disease-specific HRQOL in asthmatics with asthma symptoms, peak flow and bronchial hyperresponsiveness (1071, 1072).

Pediatric questionnaires (teen version of the pediatric quality of life inventory (PedsQL)) are available and showed an impaired QOL in adolescents with rhinitis (1073).

Impairment in the functioning of patients with moderate-to-severe perennial rhinitis (88) is comparable with the limitations perceived by asthmatic patients with a moderate-to-severe disease (1074). The extent to which asthma and rhinitis co-morbidities are associated in HRQOL has been studied in the same population (87). Both asthma and allergic rhinitis were associated with an impairment in HRQOL, but rhinitis was found to impair social life, whereas asthma mostly impaired the physical component of HRQOL.

Generic questionnaires of QOL show an improvement of QOL in patients treated with oral H_1-antihistamines and intranasal glucocorticosteroids in seasonal (1065, 1075, 1076), perennial (1077, 1078) and PER (1067). However, the improvement is usually less important than with specific questionnaires (1065, 1067).

5.3.2. Specific QOL questionnaires. Health-related quality of life questionnaires currently used to evaluate allergic disease are organ-specific. They therefore fail to take account of the systemic aspects of allergic disease. Specific instruments have been designed by asking patients what kind of problems they experience from their disease, rhinitis or conjunctivitis (1079). Both the frequency and importance of impairments find expression in the questionnaires. These instruments have the advantage of describing more accurately the disease-associated problems of the patients. Moreover, they seem to be more responsive to changes in HRQOL than generic instruments. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ; 1080) and the Rhinitis Quality of Life Questionnaire (1081) have been tested in adult patients with seasonal allergic rhinitis, perennial allergic rhinitis as well as IAR and PER. The RQLQ has been adapted to many different cultures and languages (89, 1082–1084). Specific instruments for different age groups of patients with rhinitis have also been developed (89, 90, 1085) and other questionnaires have been proposed for rhinosinusitis (222, 226, 227, 1086).

The RQLQ scores are significantly impaired in patients with moderate/severe IAR or PER by comparison with patients with mild IAR or PER (84).

The Pediatric Allergic Disease Quality of Life Questionnaire (PADQLQ) was developed in children to encapsulate problems related to the eyes, ears, nose, lungs, skin, emotions and everyday activities (1087). It was found that impairment in PADQLQ is directly related to the level of allergen exposure and allergic airway inflammation (1087). The same approach was used in asthma, and a QOL instrument assessing both asthma and rhinitis has been developed (1088). RHINASTHMA was able to differentiate patients with rhinitis from those with both rhinitis and asthma.

5.3.3. Evolution of QOL during interventions. The RQLQ has been used in several trials to assess the effect of intranasal glucocorticosteroids (1085, 1089–1094), oral H_1-antihistamines in seasonal (1095–1097), perennial (1077, 1078) and PER (1066, 1067, 1098), the combination of intranasal glucocorticosteroids and oral H_1-antihistamines (1099), leukotriene receptor antagonists (1100, 1101), allergen immunotherapy in pollinosis (1102–1104), omalizumab, an anti-IgE monoclonal antibody (768, 1105), allergen avoidance (1106) and homeopathy (1107). Studies have also been performed in children (1108).

Generally, the effect on HRQOL runs parallel with the effect on conventional medical outcome measures. However, in some studies, differences can be found indicating that patients perceive differences in efficacy, not captured by conventional symptom scores.

5.3.4. Quality of life instruments in individual patients. Although studies have shown an impairment of QOL in rhinitis in a group of patients, these questionnaires are not currently applicable for use as a clinical tool in individual patients. Inclusion of these outcome measures in the evaluation and management of the individual patient should be the next step. Moreover, there is a need for a specific instrument measuring QOL in patients with both asthma and rhinitis and, if appropriate, this questionnaire may be used as a primary outcome variable in clinical trials.

5.3.5. Health-related QOL and healthcare costs. The high prevalence of allergic rhinitis and the concern about healthcare costs justifies the increasing interest for cost-effectiveness studies. Not only the efficacy of treatment has to be demonstrated, but also the cost-effectiveness. In these studies, HRLQ measures have to be incorporated to make comparisons across patient populations and different disorders. Quality-adjusted life years associated with different medical therapies can easily be incorporated into cost-effectiveness studies.

Utility instruments are mostly generic. A recent rhinitis-specific utility, the Multiattribute Rhinitis Symptom Utility Index, has been developed for clinical trials and for cost-effectiveness studies comparing medical treatment for rhinitis (1109).

5.4. Sleep disturbance

Poorly-controlled symptoms of allergic rhinitis may contribute to sleep loss or disturbance (94, 96, 98–104). Moreover, sedation in patients with allergic rhinitis may be increased by using sedative treatments (105, 106). Although sleep apnoea syndrome has been associated with nasal disturbances (107–109), it is unclear as to whether allergic rhinitis is associated with sleep apnoea (100, 107, 110). It has been shown that patients with moderate/severe symptoms of IAR or PER suffer from impaired sleep by comparison to normal subjects and patients with mild rhinitis. All dimensions of sleep are impaired by allergic rhinitis, particularly by the moderate/severe type (111). Seasonal allergic rhinitis leads to increased daytime sleepiness (1110).

5.5. Learning disability

In children with uncontrolled allergic rhinitis, learning problems occur during school hours either by direct interference or indirectly by nocturnal sleep loss and secondary daytime fatigue (95, 114, 116). Seasonal allergic rhinitis may be associated with a reduced ability to learn (1111) and to be successful in examinations (1112). Treatment with sedating oral H_1-antihistamines will aggravate these problems, whereas treatment with nonsedating oral H_1-antihistamines will only partially reverse the limitations in learning (115, 1113).

5.6. Work impairment

It is commonly accepted that allergic rhinitis impairs work (10, 84, 113, 1114, 1115). It induces work absenteeism as well as a reduction in work productivity and presenteeism. Pollen and mold exposure impairs the work performance of employees with allergic rhinitis (1116). Nasal congestion was found to impair work productivity (1117). Work impairment is correlated with the severity of allergic rhinitis (84).

In a study in the USA (562), allergic diseases were found to be major contributors to the total cost of health-related absenteeism and presenteeism. Allergic rhinitis was the most prevalent of the selected conditions; 55% of employees reported experiencing allergic rhinitis symptoms for an average of 52.5 days, were absent for 3.6 days per year due to the condition and were unproductive for 2.3 h per work day when experiencing symptoms.

In the USA, in 1994, allergic rhinitis resulted in approximately 811 000 missed work days, 824 000 missed school days and 4 230 000 reduced activity days per year (1118).

The economic impact of work place productivity losses compared several diseases including allergic rhinitis. Allergies are major contributors to the total cost of health-related absenteeism and presenteeism. The mean total productivity (absenteeism and presenteeism) losses per employee per year were US$ 593 for allergic rhinitis which was the first most costly disease of the study (562).

The treatment of allergic rhinitis was found to improve work productivity in pollen (1119) and PER (1115), but sedative oral H_1-antihistamines reduced work productivity (1120, 1121).

Very little is known about the impact of allergic rhinitis on the career of patients. Patients may not change or lose jobs except in the case of occupational allergy (1122). On the other hand, some allergic subjects may not take part in work with a high allergen load, e.g. bakers.

5.7. The social economic impact of asthma and rhinitis

Asthma and rhinitis are chronic conditions with a substantial economic impact on the affected persons and their families, on the healthcare systems and on society as a whole. People with asthma or rhinitis must cope with both the immediate and long-term impact of a condition that often affects daily functioning. They are frequently required to make choices on how to re-allocate their personal and family resources – originally dedicated to daily needs such as food, clothing and housing – to pay for medical care aimed at improving their condition.

The world literature on the economic burden of asthma and rhinitis has only recently emerged, and to date has focused primarily on asthma because this disease was thought to present more burden than rhinitis. However, the few individual studies examining the economic impact of rhinitis also provide compelling evidence of its substantial impact (1123). Moreover, it is important to study the economic impact of rhinitis considering the patient globally with rhinitis co-morbidities (1124). Data for children are less clear and results observed in developing countries may differ from those of Western populations (1125).

5.7.1. Understanding the costs of illness. The cost-of-illness study is the tool for understanding the economic burden of illness (1126). This approach separates costs into those associated with medical-care treatments for the illness (direct costs) and those resulting from nonmedical losses as a consequence of the illness (indirect costs). Standard methods exist for placing an incremental economic value on direct medical-care costs and indirect nonmedical costs. Intangible costs, specifically those associated with the value of the psychosocial impacts of illness, have also been theorized. However, to date, the methods for valuing intangible costs have not been fully developed. Costs of illness can be viewed from the perspective of the society, the healthcare system (organizations within a community that provide or finance care) and/or the individual.

5.7.2. The costs of illness for rhinitis and its co-morbidities. Although several economic analyses of allergic rhinitis have been published, there are relatively few cost-of-illness studies outside the USA.

In the USA, in 1994, the total costs for rhinitis were estimated at $1.2 billion (1118). In 1996, direct costs for allergic rhinoconjunctivitis were $1.9 billion (1127). In another USA study, the direct medical cost of rhinitis exceeded $3 billion in 1996 and an additional cost of $4 billion resulted from co-morbidities (1128). The most recent estimates of the annual cost of allergic rhinitis range from $2 to 5 billion (2003 values; 1129). The wide range of estimates can be attributed to differences in identifying patients with allergic rhinitis, differences in cost assignment, limitations associated with available data and difficulties in assigning the indirect costs (associated with reduced productivity) of allergic rhinitis. Rhinitis increases asthma costs (1130, 1131).

The National Health Interview Survey (NHIS) was used to obtain information on the days lost from work and on lost productivity due to allergic rhinitis (1132). Wage estimates for occupations obtained from the Bureau of Labor Statistics were used to calculate the costs. Productivity losses associated with a diagnosis of allergic rhinitis in the 1995 NHIS were estimated at $601 million. When additional survey information was considered regarding the use of sedating over-the-counter (OTC) allergy medications, as well as workers' self-assessments of their reduction in at-work productivity due to allergic rhinitis, the estimated productivity loss increased dramatically. At-work productivity losses were estimated to range from $2.4 to $4.6 billion.

The cost of illness of atopic asthma and seasonal allergic rhinitis were studied in Germany (1133). Overall,

annual costs per patient increased with the severity of atopic asthma and if associated with allergic rhinitis. The average annual cost of seasonal allergic rhinitis was €1 089 per child/adolescent and €1 543 per adult.

In Ankara, Turkey, the mean cost of seasonal allergic rhinitis per person without a co-morbid disorder during the grass pollen season was around $80 without co-morbidity and reached around $140 in the presence of asthma and/or conjunctivitis (1134).

The Japanese all belong to either a government, union or community health insurance system. An accurate report of total medical expenditures can therefore be reported. For 1994, the total costs for rhinitis were $1.15 billion including direct and indirect costs as well as OTC costs. The average annual expenditure was $118 per patient (1135).

Direct medical cost parameters (medications, doctor visits and hospitalizations) and time-lost parameters [work days and Usual Daily Activities (UDA)] related to PER and its co-morbidities were measured in a prospective 6-month study comparing levocetirizine and placebo in patients with moderate/severe PER (1115). From a societal perspective, the total cost of PER without long-term treatment was estimated at €355 per patient per month. Levocetirizine reduced the total cost of PER and its co-morbidities by €153 per patient per month from a societal perspective and by €65 per patient per month from an employer perspective. Most gains resulted from a decrease in lost work days and UDA in the levocetirizine group.

5.7.3. Best economic strategies for the care of asthma and rhinitis: cost-effectiveness studies. Traditionally, medical decisions were primarily based on the evidence of clinical efficacy and safety, but resource constraints directly and indirectly affect all medical treatment decisions. Yet, presently, there is too little information available to inform patients, healthcare providers and healthcare systems as to the relative impact of various alternative treatments on resources and costs of care.

Sometimes decisions about which medical treatment or product to use are based on evidence from controlled clinical trials that focus on efficacy and safety as their specific aim. Efficacy is measured under tightly-controlled research conditions. These studies often involve very select patient populations, the results of which cannot be extended to all patients with rhinitis. Studies of clinical effectiveness have evolved in response to the need for more real-world information about treatment alternatives and patient outcomes. Effectiveness refers to the impact of the intervention or technology under routine operating conditions, administered to a more generalized patient population (1136, 1137). Improvements to the early studies of effectiveness have led to the 'cost-effectiveness' study design. This type of study design provides information on the effectiveness of various interventions in relation to the efficiency of consumption of economic resources (1138, 1139).

The increasing worldwide sensitivity to costs of care in relation to improved health benefits has not gone unnoticed in the areas of asthma and rhinitis (1140, 1141). To date, there are no clear dominant cost-effective treatment strategies for either asthma or rhinitis. However, there are studies to suggest that the use of inhaled glucocorticosteroids for people with persistent asthma is reasonably cost-effective in comparison to using only rescue ß-agonist therapy (1141). In rhinitis, the most effective drugs, e.g. intranasal glucocorticosteroids, are cost-effective when compared to less effective treatments, e.g. intranasal cromoglycate (1142). Comparisons between intranasal glucocorticosteroids are difficult because drug pricing differs between countries (1143).

The direct medical cost of rhinitis in the USA in 1999 showed that sales of prescription antihistamines and nasal steroids exceeded $3 billion and $1 billion respectively (1128). However, some of the most commonly-prescribed drugs are now OTC and the economic impact of payer policies after the prescription-to-OTC switch of second-generation oral H_1-antihistamines is of importance (1144).

The balance between safety and efficacy should be clearly assessed and it has been found that first-generation oral H_1-antihistamines are not cost-effective because of the cost of associated sedation (1145).

The economic evaluation of specific immunotherapy *vs* symptomatic treatment of allergic rhinitis was modelized in Germany and subcutaneous immunotherapy was found to be cost-effective (1146).

5.7.4. Policy implications of the economic burden of asthma and rhinitis. Healthcare decision makers such as healthcare providers and health planners are constantly faced with establishing priorities for the allocation of limited healthcare resources, especially in developing countries. This prioritization spans chronic conditions – such as asthma and rhinitis – as well as communicable diseases, and must also consider the needs for health promotion and disease prevention.

Therefore, to reduce the global burden of asthma and rhinitis, it will be necessary to first identify the degree of community-specific disease burden, and then to establish credible justification for the re-allocation of healthcare resources. The costs and benefits of introducing new asthma and rhinitis management programs must be considered not only with regard to cultural appropriateness, but also in light of the existing resources of each community. Finally, these decisions must be examined relative to what the existing resources can purchase by way of other medical care and other nonmedical goods (1140). Greater awareness of the total economic burden of allergic rhinitis should encourage appropriate intervention and ultimately ensure clinically favorable and cost-effective outcomes (1147).

Also, while much of the focus on establishing new treatment strategies must rest on the community's willingness to provide resources in most if not all

communities, some of the burden of care for both asthma and rhinitis falls upon the individuals and their families. Many people, particularly those with rhinitis, seek healing not from the healthcare practitioner, but from other sources ranging from nonprescription medications and herbal remedies to nonallopathic care providers. The individuals and their family are likely to carry much of the economic burden for this care. It is essential to further understand the value of such nontraditional approaches in comparison to allopathic care and its accompanying newer pharmacotherapeutic approaches.

5.7.5. Conclusions. Millions of people suffer physical impairments, reductions in QOL and economic consequences associated with rhinitis and its co-morbidities. Health economic studies have helped to characterize the costs of these diseases, but are limited to studies of industrialized nations. There are even fewer comparative studies by which one can judge the most efficient ways to deliver health care for these conditions. With healthcare costs increasing worldwide comes an increasing need for more advanced health economic studies if improvements are to be made to lessen the social and economic impact of these conditions.

6. Diagnosis

Diagnosis of allergic rhinitis

- The diagnosis of allergic rhinitis is based upon the concordance between a typical history of allergic symptoms and diagnostic tests.
- Typical symptoms of allergic rhinitis include rhinorrhoea, sneezing, nasal obstruction and pruritus.
- Ocular symptoms are common, in particular in patients allergic to outdoor allergens.
- Diagnostic tests are based on the demonstration of allergen-specific IgE in the skin (skin tests) or the blood (specific IgE).
- The measurement of total IgE is not useful in the diagnosis of allergic rhinitis.
- Many asymptomatic subjects can have positive skin tests and/or detectable serum-specific IgE.
- Many patients have positive tests which are clinically irrelevant.
- In some countries, the suspicion of allergic rhinitis may be addressed in the pharmacy.
- Patients with PER and/or moderate/severe symptoms of rhinitis should be referred to a doctor.
- Most patients with rhinitis are seen in primary care and, in developed countries, allergy tests are available to screen for allergy.
- Patients with PER and/or moderate/severe symptoms of rhinitis need a detailed allergy diagnosis.

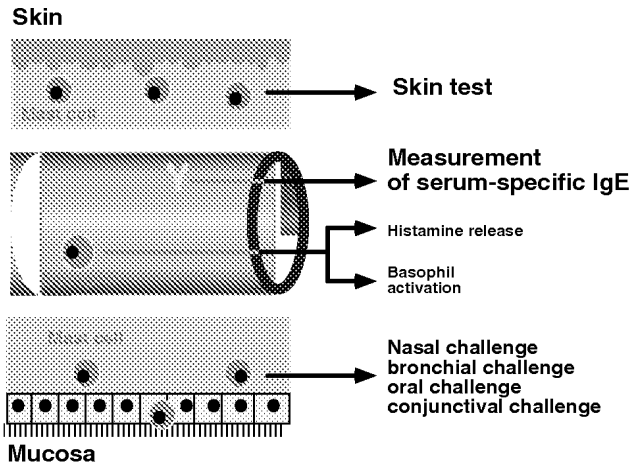

Figure 4. Diagnosis of IgE-mediated allergy.

The diagnosis of allergic rhinitis is based upon the coordination between a typical history of allergic symptoms and diagnostic tests. *In vivo* and *in vitro* tests used to diagnose allergic diseases are directed towards the detection of free or cell-bound IgE (Fig. 4).

The diagnosis of allergy has been improved by allergen standardization which provides satisfactory diagnostic vaccines for most inhalant allergens. New techniques using recombinant allergens are already available and will be of great help in the future. It appears that allergy diagnosis improves patient care (1148).

Immediate-hypersensitivity skin tests are widely used to demonstrate an IgE-mediated allergic reaction and represent a major diagnostic tool in the field of allergy (1149, 1150).

The measurement of total serum IgE has a poor predictive value for allergy screening in rhinitis and should not be used as a diagnostic tool (10). In contrast, the measurement of allergen-specific IgE in serum is of importance and has a value similar to that of skin tests (1151, 1152).

Some *in vitro* specific IgE methods use either a mixture of several allergens in a single assay (1153) or test several different allergens during a single assay. These tests can therefore be used by specialized doctors and nonallergists as screening tests for the diagnosis of allergic diseases.

Nasal and ocular challenge tests with allergens are used in research and, to a lesser extent, in clinical practice. However, they are important in the diagnosis of occupational rhinitis. Other tests have not yet been fully validated.

The tests and procedures listed below represent the spectrum of investigations, which may be used in the diagnosis of allergic rhinitis. However, only a certain number of these are routinely available or applicable to each individual patient.

6.1. History and general ENT examination

Clinical history is essential for an accurate diagnosis of rhinitis and for the assessment of its severity as well as its

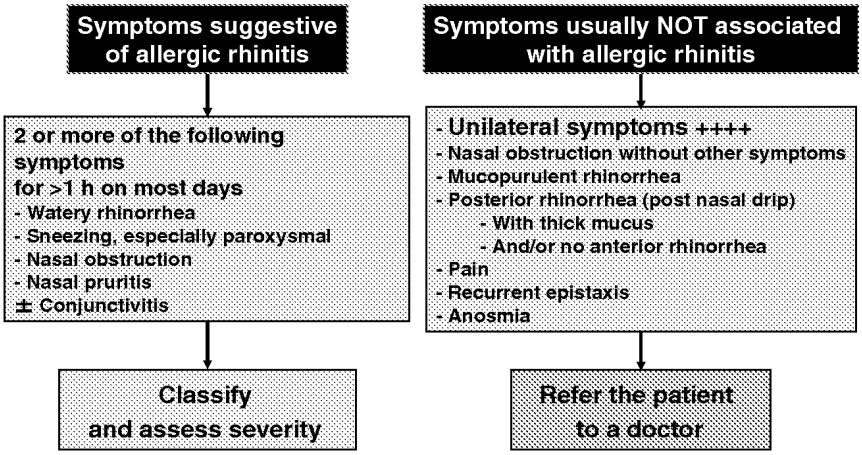

Figure 5. Symptoms of allergic rhinitis [from Ref. (1154)].

response to treatment. Patients with allergic rhinitis suffer from sneezing, anterior rhinorrhoea and very often from bilateral nasal obstruction. This is usually the most bothersome symptom in patients with allergic rhinitis. Nasal obstruction can be observed in many other conditions.

Many patients do not consult a doctor for nasal symptoms. However, some symptoms require urgent investigation (Fig. 5).

Most patients with pollen-induced rhinitis have eye symptoms. It is also important to distinguish between allergic and nonallergic symptoms (Fig. 6; Table 12).

Table 12. Symptoms and signs of allergic eye diseases [from Ref. (1155)]

Symptoms	Signs
Allergic conjunctivitis	
Tearing	Mild hyperemia
Burning	Mild edema
Itching	Mild papillary reaction (often absent)
Vernal keratoconjunctivitis	
Intense itching	Cobblestone papillae
	Intense hyperemia
Tearing	Mucous discharge
Photophobia	Milky conjunctiva
Sensation of foreign body	Punctate keratopathy
	Trantas dots
	Togby's ulcer
Atopic keratoconjunctivitis	
Itching	Hyperemia
Burning	Eczematous lesions of eyelids
Tearing	Corneal ulcers
	Cataracts
	Pannus
	Keratoconus
	Retinal detachment
Contact lens conjunctivitis	
Itching	Giant papillae
Pain	Excessive mucus production
Sensation of foreign body	Corneal lesions
Lens intolerance	

Other signs and symptoms include:

- significant loss of smell (hyposmia or anosmia), relatively infrequent in allergic rhinitis (1156–1159), but mild hyposmia is not rare;
- snoring, sleep problems (95, 102, 103, 107);
- postnasal drip or chronic cough (1160, 1161), in particular if CRS is present and
- rhinitis may induce sedation by itself (1162).

In patients with mild IAR, a nasal examination is optimal. All patients with PER should undergo nasal examination. Anterior rhinoscopy, using a speculum and mirror, provides limited information and nasal endoscopy is more useful. Nasal endoscopy is the next step which is useful in patients with treatment failure.

6.2. Skin tests

Immediate-hypersensitivity skin tests are widely used to demonstrate an IgE-mediated allergic reaction of the skin. These tests represent a major diagnostic tool in the field of allergy. If properly performed, they yield useful confirmatory evidence for a diagnosis of specific allergy. As there are many complexities in their performance and interpretation, it is recommended that they should be carried out by trained health professionals (1149). Delayed hypersensitivity tests provide little information.

6.2.1. Methods

6.2.1.1. Skin testing methods. Several methods of skin testing are available.

Scratch tests should no longer be used because of poor reproducibility and possible systemic reactions.

Prick and puncture tests are recommended for the diagnosis of immediate-type allergy because there is a high degree of correlation between symptoms and provocative challenges. The modified skin prick test introduced by Pepys (1163) is the current reference

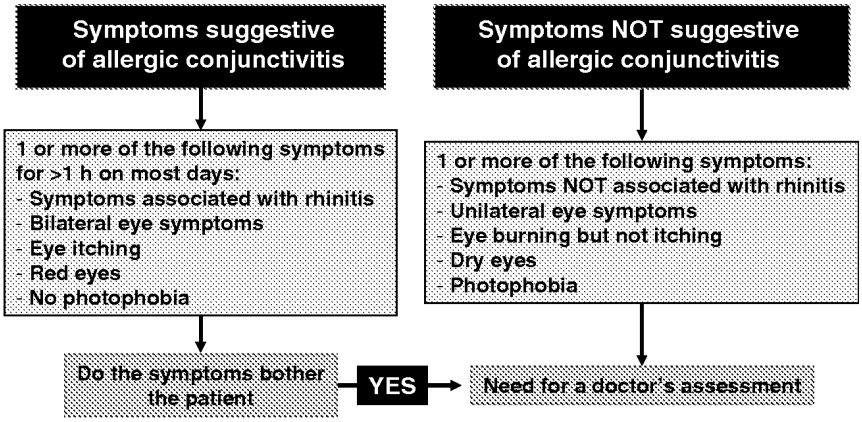

Figure 6. Symptoms of allergic conjunctivitis [from Ref. (1154)].

method. Puncture tests with various devices were introduced to decrease the variability of skin prick tests (1164–1173). With a trained investigator, they are highly reproducible (1171–1173). Prick tests should be performed according to a rigorous methodology (1174).

Intradermal skin tests may be employed for allergy diagnosis in some instances (e.g. weak allergen solution). They are not usually required for the diagnosis of inhalant allergy when standardized extracts are available (1149, 1175, 1176) as they correlate less well with symptoms (1177). They may induce some false-positive reactions. They are less safe to perform because systemic reactions can occur albeit rarely (1178, 1179).

Prick–prick tests: Prick plus prick tests with fresh foods were introduced to reduce the poor standardization of food extracts commercially available (1180–1183). Although of interest, this test is not standardized and should be restricted to foods for which no recombinant allergen is available.

Atopy patch tests involve epicutaneous patch tests with allergens known to elicit IgE-mediated reactions (1184). Commercial reagents are available for a few allergens (1185). They have been standardized regarding the use of vehicle and dose–response relationships (1186, 1187). A subset of patients with atopic dermatitis show only atopy patch test positivity while specific IgE to the same allergen remains negative. Regarding food allergy, the atopy patch test still requires standardization (1188–1190). It may also be difficult to differentiate between irritative and allergic reactions (1191).

Position Papers of the European Academy of Allergology and Clinical Immunology (EAACI; 1192), WHO (1193) and the US Joint Council of Allergy Asthma and Immunology (1194, 1195) recommend the use of skin prick-puncture tests as a major test for the diagnosis of IgE-mediated allergic diseases.

6.2.1.2. Negative and positive control solutions. Due to interpatient variability in skin reactivity, it is necessary to include negative and positive controls in every skin test study.

The **negative control solutions** are the diluents used to preserve the allergen vaccines. The rare dermographic patient will produce wheal-and-erythema reactions to the negative control. Any reaction at the negative control test sites will hinder the interpretation of the allergen sites (1194).

Positive control solutions are used to detect suppression by medications or disease and determine variations in technician performance. The usual positive control for prick-puncture testing is histamine dihydrochloride (5.43 mM or 2.7 mg/ml, equivalent to 1 mg/ml of histamine base; 1196). However, a l0-fold greater concentration is more appropriate (1197). Mast cell secretagogues such as codeine phosphate 2.5% (1168) or 9% may also be used (1198).

6.2.1.3. Skin tests with recombinant allergens. A current diagnosis of allergy relies on natural extracts that may lack standardization and/or degrade rapidly when placed in a solution. Recombinant DNA technology allows the production of pure biochemically characterized proteins. Skin tests with recombinant allergens were available in the 1990s for pollens (1199), molds such as *Aspergillus* (1200), mites (1201, 1202), venoms (1203, 1204) or latex (1205). Skin tests with recombinant and natural allergens have a similar value (1206–1210) if the recombinant allergens have been well selected and represent all or most epitopes of the natural allergen (1211–1214). Panels of recombinant allergens are available for the component-resolved diagnosis of allergy (1215).

Food allergens are usually nonstandardized and unstable in solution. Recombinant allergens are useful for the diagnosis of food allergy such as apple (525, 1216), celery (553), peanut (1217) or cherry (1218). Skin tests with recombinant food allergens can be an alternative to prick–prick tests with foods (1219).

6.2.2. Criteria of positivity. Skin tests should be read at the peak of their reaction by measuring the wheal and the flare approximately 15 min after the performance of the

tests. Late-phase reactions are not recorded because their exact significance is not known (1192, 1194, 1220).

For prick tests, when the control site is completely negative, small wheals of <3 mm represent a positive immunologic response (1163, 1221). However, these reactions do not necessarily imply the presence of a clinically relevant allergy (1149).

6.2.3. Factors affecting skin testing. Skin reaction is dependent on a number of variables that may alter the performance of the skin tests.

The quality of the allergen extract (vaccine) is of importance. When possible, allergens that are standardized by using biological methods and labeled in biological units or micrograms of major allergens should be used (1192, 1194). Recombinant allergens can also be used accurately (1208).

Age is known to affect the size of skin tests (1222) but positive skin prick tests can be found early in infancy (1223, 1224). In the elderly patient, the size of skin tests is decreased (1225, 1226).

Seasonal variations related to specific IgE antibody synthesis have been demonstrated in pollen allergy (1227). Skin sensitivity increases after the pollen season and then declines until the next season. This effect has some importance in patients with a low sensitivity (1228) and/or in patients sensitized to allergens such as cypress pollen (388).

Drugs affect skin tests and it is always necessary to question patients on the drugs they have taken. This is particularly the case for oral H_1-antihistamines, but also for other drugs which are not necessarily used for the treatment of allergic diseases (for review see Refs 1149, 1229, 1230; Table 13). Montelukast does not appear to reduce skin test reactivity (1231, 1232) and does not need to be discontinued before skin testing.

Table 13. Drugs affecting the performance of skin tests

	Suppression		
Treatment	Degree	Duration (days)	Clinical Significance
Anti-H_1 histamines			
Cetirizine	++++	3–10	Yes
Chlorpheniramine	++	1–3	Yes
Desloratadine	++++	3–10	Yes
Ebastine	++++	3–10	Yes
Hydroxyzine	+++	1–10	Yes
Levocabastine (topical)	Possible		Yes
Levocetirizine	++++	3–10	Yes
Loratadine	++++	3–10	Yes
Mequitazine	++++	3–10	Yes
Mizolastine	++++	3–10	Yes
Promethazine	++	1–3	Yes
Ketotifen	++++	>5	Yes
Anti-H_2 histamines			
Cimetidine/ranitidine	0 to +		No
Imipramines	++++	>10	Yes
Phenothiazines (132)	++	?	Yes
Glucocorticosteroids			
Systemic, short term	0		
Systemic, long term	Possible		Yes
Inhaled	0		
Topical skin	0 to ++		Yes
Theophylline	0 to +		No
Cromolyn	0		
$ß_2$-Agonists			
Inhaled	0 to +		No
Oral, injection	0 to ++		No
Formoterol	Unknown		
Salmeterol	Unknown		
Dopamine	+		
Clonidine	++		
Montelukast	0		
Specific immunotherapy	0 to ++		No

* Clinical significance for skin testing.
0 to +++: intensity of skin test suppression.

Patients with skin disease may not be tested because of dermographism (urticaria) or widespread skin lesions.

6.2.4. Interpretation of skin tests. Carefully performed and correctly interpreted, skin tests with high-quality allergen vaccines and a battery that includes all the relevant allergens of the patient's geographic area are a simple, painless and highly-efficient method. Therefore, skin testing represents one of the primary tools for allergy diagnosis by the trained doctor.

Both false-positive and false-negative skin tests may occur due to improper technique or material. False-positive skin tests may result from dermographism or may be caused by 'irritant' reactions or a nonspecific enhancement from a nearby strong reaction.

False-negative skin tests can be caused by:

- extracts of poor initial potency or subsequent loss of potency (1177);
- drugs modulating the allergic reaction;
- diseases attenuating the skin response and
- improper technique (no or weak puncture).

Even after false-positive and false-negative tests have been eliminated, the proper interpretation of results requires a thorough knowledge of the history and physical findings. A positive skin test alone does not confirm a definite clinical reactivity to an allergen.

6.3. *In vitro* tests

The discovery of IgE in 1967 was a major advance in the understanding and diagnosis of allergic diseases (1233, 1234).

6.3.1. Serum-total IgE. Serum-total IgE is measured using radioimmunoassay or enzyme immunoassay. In normal subjects, levels of IgE increase from birth (0–1 KU/l) to adolescence and then decrease slowly and reach a plateau after the age of 20–30 years. In adults, levels of over 100–150 KU/l are considered to be above normal. Allergic and parasitic diseases as well as many other conditions increase the levels of total IgE in serum (1235). Thus, the measurement of total-serum IgE should no longer be used for screening or allergy diagnosis (1, 10).

6.3.2. Serum-specific IgE using classical methods. The measurement of allergen-specific IgE in serum is of importance.

6.3.2.1. Methods and criteria of positivity. The first technique ever used to accurately measure serum-specific IgE was the radioallergosorbent test (RAST; 1236, 1237). New techniques are now available using either radiolabeled or enzyme-labeled anti-IgE (1151, 1152, 1238–1241). Results are expressed in terms of total radioactive count bounds (c.p.m.), arbitrary units (RAST class, PRU/ml) or units of IgE (IU/ml, KU/l). However, it is advisable to use a quantitative measurement (1242, 1243).

6.3.2.2. Factors affecting the measurement of serum-specific IgE. Many factors can affect the measurement of IgE (1244). The different reagents are critical for an appropriate assay (for review see Ref. 1). In particular, the anti-IgE preparations applied must be Fcϵ-specific preferably containing combinations of monoclonal antibodies with specificities against more than one epitope on the Fc fragment (1245). Calibrators should be traceable to the WHO International Reference Preparation for Human IgE, 75/502 (1245).

As for skin tests, the quality of the allergens is of critical importance and, when possible, only standardized extracts should be used.

Recombinant allergens have been used for the *in vitro* diagnosis of grass (1206, 1207, 1213, 1246, 1247), birch and Fagaleae (1248–1253), Oleaceae (1199, 1254), pollens or mites (1255–1257). A single recombinant allergen or a combination of a few major recombinant allergens can substitute the crude extract for *in vitro* diagnostic purposes (1258, 1259). Another possibility is to add some relevant recombinant allergens to an allergen extract. It also seems that the *in vitro* diagnosis for pollen allergy can be simplified using recombinant allergens. The use of a complete panel of grass allergenic molecules can mimic the current use of allergenic extracts, but new relevant information, such as an individual pattern of reactivity, adjusted prevalence and correct specific IgE concentration, can be achieved only by means of discrete allergenic molecules (1260). Panels of recombinant allergens are available for a component-resolved diagnosis of allergy (1215).

Immunoglobulin E cross-reactivity between pollen and food allergens represents the molecular basis for oral allergy syndrome. Quantitative birch-specific IgE levels proved useful in predicting clinical allergy symptoms with birch exposure (1261, 1262).

Specific IgE measurements are not influenced by drugs or skin diseases.

6.3.3. Significance of serum allergen-specific IgE. Using standardized allergen vaccines, serum-specific IgE results correlate closely to those of skin tests and nasal challenges.

As in skin tests, the presence or absence of specific IgE in the serum does not preclude symptoms, and many symptom-free subjects have serum-specific IgE.

The cut-off IgE level above which an IgE test is positive is usually 0.35 KU/l. However, some sensitized subjects have an IgE level below this cut-off, and the measurement of serum-specific IgE is usually less sensitive than skin prick tests (1263).

The cut-off IgE level above which most patients experience symptoms is still a matter of debate in inhalant (1264, 1265) and food allergy (1266–1268). Although a low specific IgE titre may not be clinically relevant, the titre of serum-specific IgE is usually unrelated with the severity of symptoms. However, wheeze and serum-specific IgE titres have been correlated in a group of subjects (1269) but the exact value of this finding in individual patients is still unclear. This is because the severity of symptoms depends not only on IgE antibodies, but also on the releasability of mediators, the response of the target organ to mediators and nonspecific hypersensitivity.

When using single allergen tests, the cost of serum-specific IgE measurement is high and only a selected list of allergens can usually be tested.

6.3.4. Serum-specific IgE using microarray technology. New options are provided by allergen microarray technology, which makes it possible to determine not only the specific antigenic protein, but also to analyse different epitopes. Such a technique has been used for inhalant and food allergens (1270–1276). Although this method is still a research tool, it has a great potential for the future component-resolved diagnosis of allergy.

6.3.5. Screening tests using serum-specific IgE. Some methods use either a mixture of several allergens in a single assay (1153, 1277–1279) or test several different allergens during a single assay (1280). These tests can therefore be used by allergy specialists and nonallergists as screening tests for the diagnosis of allergic diseases.

The clinical relevance of these tests has been extensively studied and it has been shown that their predictive value (specificity and sensitivity) in allergy diagnosis is often over 85% (1153). However, using most of these tests, the patient is defined only as allergic or nonallergic and more

extensive investigations for rhinitis are needed if the test is positive.

6.3.6. Peripheral blood activation markers. The blood basophils of allergic patients can degranulate and release mediators (histamine and CysLT) when stimulated by the specific allergen. The assay of mediators (e.g. histamine release or CysLT release), the microscopic examination of cells (e.g. basophil degranulation test) or the activation of cells can be performed. In the early 1980s, the basophil degranulation test was proposed but never fully validated (1281).

New basophil activation tests are based upon the expression of CD63 (gp53; 1282–1285), CD45 (1286) or CD203 (1287) in the presence of allergens or nonspecific stimuli measured using cytofluorimetry. These tests may be of interest in some difficult cases such as cypress pollen allergy (1288) but they require sophisticated equipment (cytofluorimetry) and further evaluation.

Recombinant allergens have also been used for histamine release (1289) and the CD63 activation of basophils. The CD63-based basophil activation test with recombinant allergens may supplement routine tests for allergy diagnosis (1290). Basophil allergen threshold sensitivity might be a useful approach to anti-IgE treatment efficacy evaluation (1287).

Tests based on CysLT release after allergen challenge may be interesting but further studies are required (1291–1293). More data are needed to fully appreciate the value of these tests.

6.3.7. Nasal-specific IgE. It has been proposed that some patients may have a local IgE immune response without any systemic release of IgE (1294, 1295), e.g. negative skin tests and serum-specific IgE. Based on current data, the concept of local allergic reaction in the nose without systemic IgE release is not fully supported (1296) and the measurement of IgE in nasal secretions cannot be routinely proposed (1297, 1298).

6.4. Nasal challenge tests

Nasal challenge tests are used in research and, to a lesser extent, in clinical practice. For standardized allergens, challenges are not usually necessary to confirm the diagnosis of inhalant allergy. However, they are important in the diagnosis of occupational rhinitis.

Recommendations on and a critical analysis of nasal provocations and methods to measure the effects of such tests have already been published (1299) by a subcommittee of the 'International Committee on Objective Assessment of the Nasal Airways'. This subcommittee has put forward guidelines for nasal provocation tests concerning indications, techniques and evaluations regarding the tests (1300; Table 14).

Table 14. Indications for nasal challenge tests [from Ref. (1300)]

1. Allergen provocations
   When there are discrepancies between the history of allergic rhinitis and tests (in cases of diagnostic doubt)
   For the diagnosis of occupational allergic rhinitis
   Before immunotherapy for allergic rhinitis although it is very rare to use nasal provocation before starting immunotherapy
   For research
2. Lysine-aspirin: nasal provocation is recommended as a substitute for oral provocation in aspirin intolerance. Whenever such a nasal provocation is negative, an oral test is still required (1301)
3. To test nonspecific hyperreactivity: nasal provocation with nonspecific stimuli (histamine, methacholine, cold dry air, kinin, capsaicin, etc.) is not relevant for daily clinical practice and diagnosis but can be used in research

6.4.1. Nasal challenge with allergen

6.4.1.1. Methods. Different methods for the provocation and measurement of nasal challenge are used. Each technique has its own advantages and restrictions. For clinical purposes, techniques for qualitative measurements may be appropriate, but for experimental research, quantitative measurements with high reproducibility are essential (1302).

The measurement of cells and mediators in the nose may increase the sensitivity of nasal challenges (1303–1306) but more data are needed.

Factors affecting nasal challenge. As in other *in vivo* tests, the major factors affecting nasal challenge are the quality of the allergens used as well as the drugs taken by the patient. Sodium cromoglycate and usual oral H_1-antihistamines should be withdrawn 48 h before the test and intranasal glucocorticosteroids 3–6 days before. Nasal vasoconstrictors modify nasal airflow but do not have any effect on sneezing or mediator release and cell infiltration during nasal challenge. Specific immunotherapy decreases the sensitivity of the nose to allergens.

Moreover, other factors are more specific to nasal challenge, including technical problems and inflammation of the nasal mucosa (1). An allergic reaction significantly increases the reactivity of the nose because of the priming effect initially described by Connell (72, 74, 1307–1309). This effect may be seen for up to 6 weeks.

Viral infections induce the release of histamine (1310) and proinflammatory mediators such as CystLT and cytokines in nasal secretions. Nasal challenges should thus be performed at least 2–4 weeks after any allergic or infectious episode.

Finally, the nasal cycle (1311) should be taken into consideration when rhinomanometry is used.

6.4.1.2. Nasal challenge with nonspecific agents. Nonspecific nasal hyperreactivity is commonly observed in patients with allergic rhinitis (784, 832, 838, 1312). Challenges with methacholine or histamine have been widely carried out. Methacholine and histamine both

induce a dose-dependent increase in secretion weights on the challenge site, whereas histamine alone induces a contralateral reflex. Repeated stimulation with histamine, but not methacholine, results in tachyphylaxis (1313).

6.4.2. Challenge with occupational agents. The diagnosis of occupational rhinitis is often complex and requires nasal provocation tests with the relevant occupational agent (144, 1314–1318). The challenge can be carried out in the form of a natural exposure, especially if the relevant allergen is unavailable. As an example, this has been done for laboratory animal allergy in a vivarium during cage cleaning (high-allergen challenge), quiet sitting (low-allergen challenge) and in a remote location (sham challenge) (1319).

6.5. Environmental exposure units

There is an increasing need for allergen inhalation systems to perform basic clinical research and test antiallergic drugs under well-controlled conditions. This requires stable environmental conditions (e.g. temperature and humidity), as well as allergen concentration and the reproducible induction of allergic symptoms. Nasal, ocular and bronchial symptoms can be measured.

Pollen exposure in the environmental exposure unit is an effective, reproducible, safe and suitable method for single-center clinical studies (1320–1323). These exposure units are mostly used to assess the efficacy of antiallergic treatments. However, there are pitfalls in these studies because the priming effect on the nasal mucosa is not considered in most studies (72, 74, 1307–1309) and the results of the challenges may not accord with the clinical data obtained from RCTs. These chambers are commonly used to assess the onset of action of medications.

Park studies have been used to assess the onset and magnitude of efficacy of treatments for pollen-induced allergic rhinitis (1324, 1325).

In cat allergy, exposure to cats in environmental exposure units has been widely used (1326–1329) but there is a high variability of cat allergen during the study.

The Vienna chamber was also used in mite allergy (1330).

There are also environmental exposure units which are used for the diagnosis of occupational allergy. These are of great value and have been used, for example, for latex sensitization (1331, 1332).

6.6. Other tests

6.6.1. Mediators released during allergic reactions. The measurement of mediators such as histamine, PGD_2, CysLTs, kinins, tryptase and ECP released into peripheral blood, nasal secretions or urine during provocation challenge or an allergic reaction represents a research tool.

6.6.2. Cytology and histology. Nasal cytology and histology usually represent a research tool.

6.6.3. Measurement of nitric oxide in exhaled air. Measurements of nasal nitric oxide (nNO) are attractive because they are completely noninvasive and can easily be performed (1333–1337). The measurements may be useful in the early diagnosis of patients with chronic airway disorders such as Kartagener's syndrome and cystic fibrosis in which low levels are found (1338–1340). The possible use of nNO measurements in the diagnosis and treatment of allergic rhinitis still needs to be further evaluated because of the variable and also contradictory findings of nNO concentrations in this disease (123, 1337, 1341–1343).

6.7. Diagnosis of immediate-type allergy

The diagnosis of allergy is based on the correlation between the clinical history and tests. No possible diagnosis can be based only on responses to skin tests, *in vitro* tests or even challenges (1344). Factors affecting tests should always be checked before investigations and particularly treatments, as some may modify the results of *in vivo* tests for several days. For these reasons, patients may benefit more from skin testing by specially-trained health professionals.

Allergic rhinitis is a growing primary care challenge because most patients consult primary care doctors (1345). General practitioners play a major role in the management of allergic rhinitis as they make the diagnosis, start the treatment, give the relevant information and monitor most of the patients (113). In some countries, general practitioners perform skin prick tests. Studies in the Netherlands and the UK found that common nasal allergies can be diagnosed with a high certainty using simple diagnostic criteria (1346, 1347).

However, with the large use of OTC drugs, many patients do not consult a doctor for their nasal symptoms and buy their drugs in the pharmacy, although there are large differences between countries regarding the role of the pharmacist. Finally, a large number of patients are not aware of their rhinitis and do not receive any treatment.

6.7.1. Asymptomatic-sensitized subjects. The occurrence of positive responses to skin tests or the presence of specific IgE (1348) does not necessarily imply that the IgE-mediated allergy is related to symptoms, as skin prick tests are positive in up to 43% of symptom-free individuals depending on the allergen, the skin test method, the area and the population studied (patients or general population; 1349–1355). Using passive transfer tests, it was shown that these antibodies were functional (1349, 1350). In the general population (Dutch ECRHS study), 43% of the subjects with IgE to inhalant allergens did not have any respiratory symptoms (289, 1355). In longitudinal studies, the presence of positive skin tests in

nonsymptomatic subjects predicts the onset of allergic symptoms including asthma (1042, 1356–1360), especially if the allergen load is high. The optimal cut-off values for clinically relevant skin prick test results have been reported for some inhalant allergens (1264, 1265) but more data are needed.

6.7.2. Mono and polysensitized subjects. Exposed to a common environment, the IgE-mediated immune response differs among sensitized subjects. Some of them react to one allergen (monosensitized), whereas others are sensitized to many allergens (polysensitized) (387, 1361–1363). Taking into consideration cross-reactivities between allergens and panallergens (525, 557, 1364), a minority of symptomatic patients are sensitized to a single allergen (monosensitized; 1362).

Monosensitized patients often appear to be either children who may develop polysensitization later in life or adults who will only develop a single allergenic sensitivity (388, 1365, 1366).

Many polysensitized patients have clinically irrelevant positive skin tests and/or specific IgE because the patient clinically reacts to some allergens only or because panallergens explain cross-reactive positivities. This is why it is essential to confront the results of skin tests and/or specific IgE with the timing of allergen exposure. Allergy diagnosis based on allergenic molecules is important for the detection of panallergens or multiple allergen reactivities (1367).

6.7.3. Correlation between tests. Serum-specific IgE, skin prick tests and allergen challenge do not have the same biological and clinical relevance and are not interchangeable (55, 1368).

Skin tests represent the primary diagnostic tools used for immediate-type hypersensitivity for doctors who are trained to perform and interpret them.

Comparisons between the measurement of specific IgE and skin tests depend on the quality and standardization of the allergens used in both types of tests and, to a lesser extent, on the method of skin testing used. The worst correlations have been obtained with mold, food extracts and unstandardized extracts. There are significant correlations between a strongly positive response to a skin test and the detection of serum-specific IgE and between a negative response to a prick test and the lack of detection of serum-specific IgE. However, small wheals induced by prick tests and positive results of intradermal tests with concentrated extracts are less frequently associated with the detection of serum-specific IgE (56, 1369). Moreover, low levels of serum-specific IgE are less often associated with symptoms than higher levels, but they do not exclude allergic symptoms (1243, 1370). Correlations between responses to skin tests or serum-specific IgE and nasal challenges are less consistent because of the nonspecific hyperreactivity.

There is usually a lack of correlation between titres of serum allergen-specific IgE and symptoms in untreated patients with seasonal allergic rhinitis (1371).

6.7.4. Diagnosis of inhalant allergy. The diagnosis of allergic rhinitis should reflect the differences in practices and, where applicable, should help pharmacists to advise their patients.

With inhalant allergens, skin test responses represent one of the first-line diagnostic methods and when they correlate with the clinical history, *in vitro* tests may not be required (1192, 1194, 1344, 1372, 1373). The costs of each procedure need to be considered (1374, 1375). The decision to initiate diagnostic testing must rely on clinical judgment to select patients who would benefit most from determining their allergic status while minimizing unnecessary testing and medication (1376).

The diagnosis of inhalant allergy differs in specialist and general practices (1346, 1347).

In most specialist practices, skin tests represent the first diagnostic method in patients with a suggestive clinical history. If there is a correlation between the occurrence of symptoms and skin tests, serum-specific IgE and challenges are not usually needed. If there are discrepancies or multiple allergen sensitivities, serum IgE and eventually nasal challenges may help to better characterize patients.

In general practice, skin tests are rarely available and a specific IgE screening is carried out. If positive, the doctor may request specialist advice for the exact diagnosis of allergen sensitization. It has recently been shown that, in general practice, common nasal allergies can be diagnosed efficiently with the aid of simple diagnostic criteria using either skin prick tests or serum-specific IgE (1346).

Some patients visiting the pharmacy will have had allergic rhinitis previously diagnosed by a doctor, others will have made an appropriate self-diagnosis and some will not have any diagnosis of rhinitis or may even have an incorrect diagnosis (e.g. a viral infection, cold or a severe nasal condition requiring rapid recognition). The pharmacist should always therefore ask patients to give an account of his or her symptoms to assist in recognizing the disease and assessing the severity. The most commonly reported symptoms are sneezing and an itchy, congested nose (nasal blockage) as well as a runny nose (nasal discharge or rhinorrhoea) (1377, 1378). If the patient does not provide sufficient information about symptoms to determine a diagnosis, more information can be elicited by structured questioning (Table 15).

Nurses may also play an important role in the identification of allergic diseases including allergic rhinitis in the primary care of developing countries and in schools.

Table 15. Questions to elicit information

What is your main symptom? (Check for rhinorrhoea, sneezing, itchy nose, nasal congestion and/or obstruction, watery or itchy eyes.)
Has a doctor ever diagnosed that you have hay fever, allergic rhinitis or asthma?
How long have you had these symptoms?
Do you have the symptoms all the time or do they come and go?
Are you aware of anything that seems to bring the symptoms on, such as being outdoors, around animals or related to something you handle at work or at home?
Is your nasal discharge clear and watery? (purulent discharge suggests infection)
Do you have an earache or pain in your face? ('Yes' may indicate otitis media or sinusitis.)
Do you have eye symptoms?
Do you have a family member with allergy problems?
What medications have you already tried for these symptoms?
Do you have any other medical conditions or are you on any other medication?

Allergic rhinitis produces symptoms similar to those of a number of other conditions and may be confused with a viral infection such as the common cold and with chronic sinusitis. Figure 7 presents a symptom-based algorithm for differentiating allergic rhinitis from another cause or infectious disease.

6.7.5. Diagnosis of food allergy. Tests for IgE-mediated food allergy include skin prick tests and the measurement of serum allergen-specific IgE antibodies (1266, 1268, 1379, 1380). However, the diagnosis of food allergy is compounded because currently-available allergen vaccines and test reagents are not standardized and their stability is poorly determined (195, 1381, 1382). Recombinant allergens improve the diagnosis of food allergy (1217). The presence of food-specific IgE in serum or a positive skin test to a foodstuff does not always correlate with food allergic symptoms because many patients outgrow their allergy with age (1383, 1384) and not all patients with food-specific IgE have a clinical sensitivity (1385). In many instances, the diagnosis has to be confirmed by a double-blind food challenge that should be carried out under precisely specified conditions (1386–1388) and by trained staff who have the competence to manage anaphylactic reactions. As for other forms of allergy, unproven and controversial techniques such as food-specific IgG or cytotoxic tests have no proven value (1).

Many patients with pollen allergy develop fruit and vegetable allergy because of the cross-reactivity between allergens, but there are large differences between patients (1389).

6.7.6. Diagnosis of occupational allergy. Occupational rhinitis must be more precisely confirmed than allergic rhinitis of other etiology. In practice, interviews concerning the causal relation, frequency, latent period and atopic disposition often provide suggestions but sometimes give unreliable evidence to base the diagnosis of occupational nasal allergy. Therefore, nasal provocation tests (144, 1314–1317) are necessary to confirm the causality between the disease and any work exposure (1390).

6.8. Other ENT diagnoses

6.8.1. Bacteriology. Routine swabs for bacterial culture taken blindly from the nose and nostrils are not

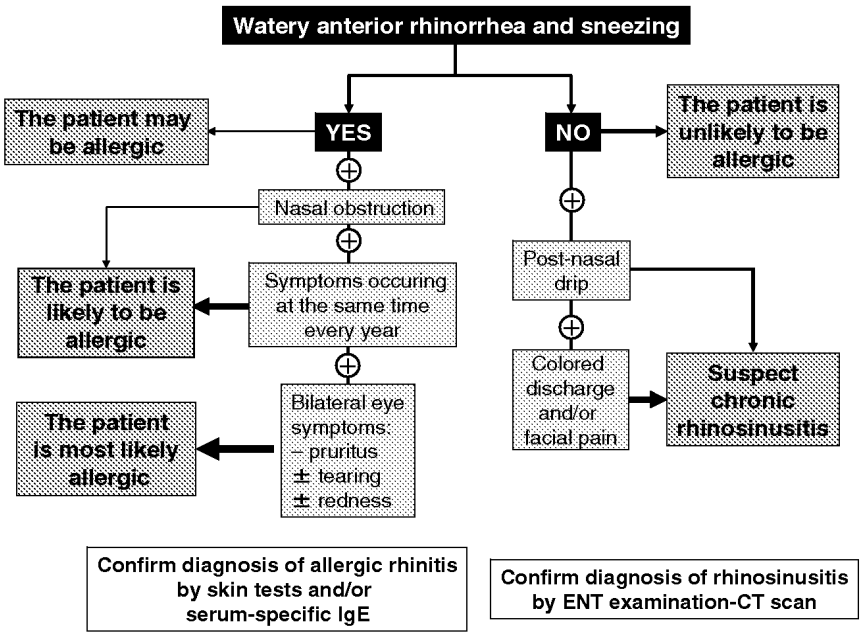

Figure 7. Diagnosis algorithm of allergic rhinitis. This figure does not apply to preschool children. Some patients with allergic rhinitis may only have nasal obstruction as a cardinal symptom. Some patients with mild allergic rhinitis may have dissociated symptoms of rhinorrhoea, sneezing and nasal obstruction.

diagnostically helpful. This may not be the case if the swabs are taken endoscopically from the middle meatus.

6.8.2. Nasal endoscopy. The availability of nasal endoscopes enables the doctor to visualize the posterior nasal cavity and the middle meatus (1391).

6.8.3. Imaging. Plain sinus radiographs are not indicated in the diagnosis of allergic rhinitis or rhinosinusitis.

Computerized tomography has become the principal radiological investigation for major sinonasal disorders but is of limited use in the diagnosis of allergic rhinitis (1392–1396). Computerized tomography scans can be carried out after receiving specialist advice:

- to eliminate other conditions;
- to exclude CRS, especially after nasal examination with optical devices;
- to eliminate complications in rhinitis;
- in patients who do not respond to treatment and
- in patients with unilateral rhinitis.

Magnetic resonance imaging (MRI; 1397) is rarely indicated as a diagnostic tool. However, there are circumstances where MRI is useful, in particular in fungal sinusitis, tumors and encephaloceles.

6.8.4. Mucociliary function. Tests for mucociliary clearance or ciliary beat frequency have little relevance in the diagnosis of allergic rhinitis but are relevant in the differential diagnosis of chronic rhinorrhoea in children and in immotile cilia syndrome.

6.9. Assessment of the severity and control of rhinitis

For asthma, there are objective measures of severity such as pulmonary function tests and well-defined criteria for symptom severity (1140). More recently, control tests based on a few symptoms and reliever medication requirements have been proposed. For atopic dermatitis, there are validated clinical scores of severity such as SCORAD (1398). For asthma, control tests are also available (1399, 1400). However, for allergic rhinitis, control questionnaires or methods are still undergoing validation.

6.9.1. Control questionnaires and visual analogue tests. Several groups are attempting to propose rhinitis control questionnaires. The ARIA scoring system uses several questions and cannot be quantified. Moreover, when applied to general practices, a more simple evaluation is favored. Visual analogue scales are quantitative measures largely validated in many diseases (1401, 1402). The scales have been extensively used to assess the severity of rhinitis (728, 1403–1406) as well as the efficacy of therapeutic interventions (118, 1406–1410). The VAS was proposed by the Joint Task Force on Practice Parameters for the symptom severity assessment of allergic rhinitis (118). This Task Force proposed to use several VAS to account for the different symptoms of allergic rhinitis because some, such as nasal congestion, may be more relevant to rhinitis severity (1117). On the other hand, several VAS scores may be difficult to combine and a single VAS scale was used to assess the global perception of rhinitis severity in general practices. It was found to correlate very well with the severity assessed by ARIA (119).

As in asthma (67), the control of rhinitis symptoms is independent of treatment (119).

6.9.2. Objective measures of severity. Routine measurements of nasal obstruction and smell measurements are used. Reactivity measurements include provocation with histamine, methacholine, allergen, hypertonic saline, capsaicin or cold dry air (124). Nitric oxide measurement and other measures are primarily used in research.

6.9.2.1. Measurement of nasal obstruction. Nasal obstruction is difficult to quantify directly by clinical examination, so objective assessments such as PNIF, rhinomanometry and acoustic rhinometry are used (120–122). In daily practice, PNIF is attracting more and more attention, because it is simple, cheap, fast and readily available (122, 1411). Moreover, PNIF is reproducible and related to the signs of rhinitis, as determined by clinical examination (122). The PNIF provides information that is qualitatively different to that provided by symptom scores and may be useful to measure the extent of nasal obstruction.

6.9.2.2. Olfactory tests. Olfaction can be measured objectively (Electro-Olfactogram and Olfactory Event-Related Potentials) or subjectively. Subjective tests can be divided into tests measuring odor threshold, odor discrimination and odor identification. For Europe, the Zurcher smell test and the 'Sniffin' Sticks' test are the most commonly used. The American UPSIT is less useful because some of the smells used are uncommon in Europe (1412). The Zurcher smell test is a simple identification test with eight smell discs. Because of the small number of discs, simulators cannot be found. The 'Sniffin' Sticks' smell test uses pen-like odor dispensing devices (1413). There is a simpler test containing 12 sticks and a very extensive one using 112 sticks. The test is well validated in Europe (1414). As olfactory tests depend on different cultures and societies (e.g. food, fragrances and education), a 'Mediterranean' olfactory test (BAST-24) has also been developed (1415).

7. Management

Recent advances in our understanding of the mechanisms underlying inflammation of the upper and lower airways have led to improved therapeutic strategies for the management of allergic rhinitis. Practice guidelines incorporating these advances have been developed (1, 9, 21, 59, 1377). In addition, a new classification of allergic rhinitis aids the establishment of an appropriate initial treatment strategy based on the duration and intensity of the patient's symptoms and lifestyle limitations (1, 21, 1155).

Many patients suffering from allergic rhinitis do not recognize the process as such, do not consult a doctor (1155, 1377) and only use OTC drugs. Others commonly seek self-treatment for the relief of symptoms and use unproven therapies. It is therefore very important to recognize the signs and symptoms suggestive of moderate/severe rhinitis or of a differential diagnosis of allergic rhinitis that may require urgent medical management (1154).

The management of allergic rhinitis encompasses patient education, pharmacotherapy and allergen-specific immunotherapy. Surgery may be used as an adjunctive intervention in a few highly-selected patients (1, 1154, 1193). Environmental control is more controversial (1416).

'Evidence-based medicine' (EBM) is an increasingly important concept which has become a new paradigm in medicine (1417). The increasing influence of EBM, due partly to the work of the Cochrane Collaboration, has led the way in setting new standards for preparing clinical recommendations (1418).

In the first ARIA document, it was recommended to propose a strategy combining the treatment of both upper and lower airway disease in terms of efficacy and safety (1).

The ARIA update is also evidence based, on Shekelle et al. (12). However, most trials were carried out before the new classification of allergic rhinitis was made and are reported for seasonal and perennial rhinitis.

The World Health Organization, like many other organizations around the world, has recognized the need to use rigorous processes to ensure that healthcare recommendations are informed by the best available research evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (22) is currently suggested in the Guidelines for WHO Guidelines and is being used by an increasing number of other organizations internationally (1419). Moreover, WHO is now proposing to use the Appraisal of Guideline Research & Evaluation (AGREE) instrument (1420) to meet the basic quality requirements for guidelines. The AGREE (1420) and GRADE approaches (1421–1423) were not used in this update but they are currently being used for a future Revision of ARIA.

7.1. Environmental control

Tertiary environmental control

- The majority of single preventive measures of indoor allergen control fail to achieve a clinically relevant improvement of asthma and rhinitis.
- Standard procedures for the control of indoor allergens in the tertiary prevention of rhinitis or asthma are not advisable for public health.
- In patients allergic to animals with fur who have symptoms on contact with the allergen, animal avoidance is recommended.
- In low-income settings with a high load of pollutants (and allergens), a multifaceted intervention may be useful.
- Total avoidance of occupational agents is recommended in sensitized subjects.
- Occupational agent control may be useful when total avoidance is not possible.

7.1.1. Levels of prevention. Three levels of prevention can be considered (1424):

Primary prevention can be defined as the protection of health by personal and community-wide effects, e.g. preserving good nutritional status, physical fitness and emotional well-being, immunizing against infectious diseases and making the environment safe. In the case of allergy, primary prevention is employed in situations where there is no evidence of allergic sensitization focused on populations at a high risk of becoming sensitized (1425).

Secondary prevention can be defined as the measures available to individuals and populations for the early detection and prompt and effective intervention to correct departures from good health. In the case of allergy, secondary prevention is employed in individuals who show evidence of sensitization to allergens but not yet any evidence of disease.

Tertiary prevention consists of the measures available to reduce or eliminate long-term impairments and disabilities, to minimize suffering caused by existing departures from good health and to promote the patient's adjustment to irremediable conditions. This extends the concept of prevention to the field of rehabilitation (WHO: Ottawa Charter for Health Promotion. Geneva: WHO, 1986). In the case of allergy, tertiary prevention will involve preventive strategies for the management of established allergic rhinitis or asthma. Inevitably, most published work comes from tertiary prophylaxis.

7.1.2. Inhalant-allergen avoidance. A range of inhalant allergens has been associated with allergic rhinitis, of which HDM is the most important and most investigated (1426, 1427). Most allergen-avoidance studies have dealt with asthma symptoms and very few have studied rhinitis symptoms. Unfortunately, the majority of interventions have failed to achieve a sufficient reduction in allergen load to enhance any clinical improvement (1428).

A systematic review of dust mite allergen avoidance has shown that single measures are not effective in reducing symptoms of allergic rhinitis (1429). A similar review was published for asthma (1430). Only seven rhinitis trials satisfied the inclusion criteria, five of which were small and judged to be of poor quality. There was no significant beneficial effect from physical or chemical interventions. A large study investigated the effectiveness of mite allergen-impermeable encasings in mite-sensitized patients with perennial rhinitis and a positive nasal challenge test to mite extract (1410, 1431). The active covers reduced the level of mattress Der p 1 to approximately 30% of the baseline level, whereas the placebo covers had no effect. However, there was no difference between groups in any of the outcome measures.

Two small studies have addressed the effects of pet allergen-control measures in rhinitis. In a randomized-controlled trial (RCT) of the efficacy of High Efficiency Particulate Air (HEPA) filters, nasal symptoms did not differ between active intervention and the placebo group (1432). In another study, a set of allergen-control measures (washing all walls and floors, removing carpeting from bedrooms, applying tannic acid, washing bedding, replacing duvets and pillows, using impermeable covers, washing the cat every 2 weeks, etc.) resulted in a fall in the Fel d 1 level to 6.8% of the baseline and in a significant improvement in nasal symptoms and nasal peak flow (1433).

Although the general consensus is that allergen avoidance should lead to an improvement of symptoms, there is very little evidence to support the use of single physical or chemical methods (Table 16). Recommendations proposing their use are at variance with the current evidence (24, 1416). The use of mattress encasings or HEPA filters as a single intervention for HDM and pet allergy in adults with asthma or rhinitis cannot be advocated. Considering the management of allergy, current evidence suggests that interventions in children (either single or multifaceted) may be associated with at best a minor beneficial effect on asthma control. However, no conclusive evidence exists regarding rhinitis or eczema. There is a need for an adequately-designed trial assessing the effects of a multifaceted intervention in this age group (1434). However, multifaceted avoidance measures might be helpful for some highly-selected patients after environmental counseling.

Patients allergic to animals with fur may benefit from allergen avoidance at home, but they may encounter allergens in public transportation, schools and public places (see Chapter 3.4.1.4). The real value of such avoidance needs further studies.

Table 16. Effectiveness of avoidance measures in rhinitis and asthma for certain indoor allergens [adapted from Ref. (24)]

Measure	Evidence of effect on allergen levels	Evidence of clinical benefit
House dust mites		
Encase bedding in impermeable covers	Some	None (adults): Evidence A Some (children): Evidence B
Wash bedding on a hot cycle (55–60°C)	Some	None: Evidence A
Replace carpets with hard flooring	Some	None: evidence A
Acaricides and/or tannic acid	Weak	None: Evidence A
Minimize objects that accumulate dust	None	None: Evidence B
Use vacuum cleaners with integral HEPA filter and double-thickness bags	Weak	None: Evidence B
Remove, hot wash or freeze soft toys	None	None: Evidence B
Pets		
Remove cat/dog from the home	Weak	None: Evidence B
Keep pet from main living areas/bedrooms	Weak	None: Evidence B
Use HEPA-filter air cleaners	Some	None: Evidence B
Wash pet	Weak	None: Evidence B
Replace carpets with hard flooring	None	None: Evidence B
Use vacuum cleaners with integral HEPA filter and double-thickness bags	None	None: Evidence B
Set of allergen control measures	Some	Some: Evidence B

Evidence from Shekelle et al. (12).

7.1.3. Other measures

7.1.3.1. Occupational agents. Many agents are involved in the development of rhinitis and asthma. It is recommended to completely avoid the occupational agent when a subject is sensitized, and data are available for occupational asthma. However, the reduction in allergens may not be sufficient and studies in latex allergy are usually of a small size or are hampered by methodological issues preventing a strong recommendation (137, 1435).

An early diagnosis of the disease is needed for the tertiary prevention of OADs since the earlier the worker is removed from the workplace, the more likely he/she will be cured (1436). Moreover, after some years of exposure, intractable asthma may persist even after work cessation. Tertiary prevention usually requires complete avoidance from the risk. However, in some cases such as latex, the use of gloves containing very low levels of allergen (e.g. nonpowdered gloves) may permit allergic healthcare workers to continue their work (1437). The risk of an increased sensitization may result from continuous exposure.

A few reports indicate that air supply helmet respirators may be safely used for occasional work in areas of potential exposure (1438, 1439).

Tertiary prevention should not apply for irritant-induced OAD for which measures to reduce the likelihood of accidental inhalation episodes should be proposed (559).

7.1.3.2. Indoor and outdoor air pollutants. Air pollutants are commonly associated with nonallergic rhinitis and may exacerbate patients with allergic rhinitis. On the other hand, tobacco smoke does not appear to aggravate the symptoms of allergic rhinitis.

Multifaceted allergen and irritant avoidance measures were found to inconstantly reduce asthma symptoms in a group of children living in poverty areas who were often inadequately treated (1440–1443). No effect on rhinitis was reported. Applying allergen avoidance as a treatment for asthma among children living in poverty is difficult because of multiple sensitivities and problems applying the protocols in this type of environment. The current results demonstrate that home visiting positively influences the management of asthma among families living in poverty (1444). No recommendation can be made, even for inner-city asthma.

The right to breathe healthy air in dwellings was recognized as a fundamental right by WHO in 2000. The Towards Healthy Air in Dwellings in Europe project has been promoted by EFA with the support of the European Commission (1445). Recommendations for an action plan to prevent the adverse effects of poor air quality in dwellings include:

- improve ventilation;
- improve cleaning methods and housing hygiene;
- avoid wall-to-wall carpeting;
- use moisture control to prevent the accumulation of mold and
- control the sources of pollution, e.g. tobacco smoke and emissions from buildings and consumer products.

However, no existing study demonstrates that environmental control measures are beneficial due to methodological problems (Evidence B).

7.2. Drug treatment

Pharmacotherapy of allergic rhinitis and conjunctivitis

- Second-generation oral or intranasal H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis in adults and children.
- First-generation oral H_1-antihistamines are not recommended when second-generation ones are available, due to safety concerns.
- Topical H_1-antihistamines are recommended for the treatment of allergic rhinitis and conjunctivitis.
- Intranasal glucocorticosteroids are recommended for the treatment of allergic rhinitis in adults and children. They are the most effective drugs for the treatment of allergic rhinitis.
- Intramuscular glucocorticosteroids and the long-term use of oral glucocorticosteroids are not recommended due to safety concerns.
- Topical cromones are recommended in the treatment of allergic rhinitis and conjunctivitis, but they are only modestly effective.
- Montelukast is recommended in the treatment of seasonal allergic rhinitis in patients over 6 years of age.
- Intranasal ipratropium is recommended for the treatment of rhinorrhoea associated with allergic rhinitis.
- Intranasal decongestants may be used for a short period of time in patients with severe nasal obstruction.
- Oral decongestants (and their combination with oral H_1-antihistamines) may be used in the treatment of allergic rhinitis in adults, but side effects are common.
- The treatment of allergic rhinitis should consider the severity and duration of the disease, the patient's preference, as well as the efficacy, availability and cost of medications.
- A stepwise approach depending on the severity and duration of rhinitis is proposed.
- A tailored approach is needed for each individual patient.
- Not all patients with moderate/severe allergic rhinitis are controlled despite optimal pharmacotherapy.

Pharmacologic treatment should take the following factors into account:

- efficacy;
- safety;
- cost-effectiveness of medications;
- patient's preference;
- objective of the treatment (26, 1446–1448);
- likely adherence to recommendations (1406);
- severity and control of the disease and
- the presence of co-morbidities.

Medications used for rhinitis are most commonly administered intranasally or orally. The efficacy of medications may differ between patients. Medications have no long-lasting effect when stopped. Therefore, in PER, maintenance treatment is required. Tachyphylaxis does not usually occur with prolonged treatment. Certain studies have compared the relative efficacy of these medications and have found that intranasal glucocorticosteroids are the most effective (1449).

Reviews of medications for the treatment of allergic rhinitis have recently been published and details on drugs are provided (26, 1450, 1451; Table 17).

Table 17. Glossary of medications used in allergic rhinitis [adapted from Ref. (1155)]

Name and also known as	Generic name	Mechanism of action	Side effects	Comments
Oral H_1-antihistamines	**Second generation** Acrivastine (1452–1454) Azelastine (1455) Cetirizine (1456–1460) Desloratadine (1461–1464) Ebastine (1465–1467) Fexofenadine (1468–1471) Levocetirizine (1066, 1108, 1472) Loratadine (1473, 1474) Mequitazine (1475, 1476) Mizolastine (1477, 1478) Rupatadine (1479–1481) **First generation** Chlorphenyramine (1476, 1482) Clemastine (1483) Dimethindene maleate (1484) Hydroxyzine Ketotifen (1485) Oxatomine (1485, 1486) **Cardiotoxic*** Astemizole Terfenadine	Blockage of H_1 receptor Some antiallergic activity New generation drugs can be used OD No development of tachyphylaxis	**New generation** No sedation for most drugs No anticholinergic effect No cardiotoxicity for products still available Acrivastine has sedative effects Mequitazine has an anticholinergic effect Oral azelastine may induce sedation and a bitter taste **Old generation** Sedation is common And/or anticholinergic effect	New generation oral H_1-antihistamines should be preferred for their favorable efficacy/safety ratio and pharmacokinetics Rapidly effective (<1 h) on nasal and ocular symptoms Moderately effective on nasal congestion Cardiotoxic drugs are no longer marketed in most countries*
Local H_1-antihistamines (intranasal, intraocular)	Azelastine (1487–1490) Levocabastine (1491–1494) Olopatadine (1495, 1496)	Blockage of H_1 receptor Some antiallergic activity for azelastine	Minor local side effects Azelastine: bitter taste	Rapidly effective (<30 min) on nasal or ocular symptoms
Intranasal glucocorticosteroids	Beclomethasone dipropionate (1497–1499) Budesonide (1500–1502) Ciclesonide (1503, 1504) Flunisolide (1505, 1506) Fluticasone propionate (1099, 1325, 1507–1509) Fluticasone furoate (1510, 1511) Mometasone furoate (1512–1516) Triamcinolone acetonide (1517–1520)	Potently reduce nasal inflammation Reduce nasal hyperreactivity	Minor local side effects Wide margin for systemic side effects Growth concerns with BDP only In young children consider the combination of intranasal and inhaled drugs	The most effective pharmacologic treatment of allergic rhinitis Effective on nasal congestion Effective on smell Effect observed after 12 h but maximal effect after a few days
Leukotriene antagonists	Montelukast (1100, 1521–1523) Pranlukast Zafirlukast	Block CystLT receptor	Excellent tolerance	Effective on rhinitis and asthma Effective on all symptoms of rhinitis and on ocular symptoms
Local cromones (intranasal, intraocular)	Cromoglycate (1505, 1524) Nedocromil (1525–1527) NAAGA (1528)	Mechanism of action poorly known	Minor local side effects	Intraocular cromones are very effective Intranasal cromones are less effective and their effect is short lasting Overall excellent safety
Oral decongestants	Ephedrine Phenylephrine Phenyl propanolamine Pseudoephedrine **Oral H_1-antihistamine–decongestant combination**s (1529–1534)	Sympathomimetic drugs Relieve symptoms of nasal congestion	Hypertension Palpitations Restlessness Agitation Tremor Insomnia Headache Dry mucous membranes Urinary retention Exacerbation of glaucoma or thyrotoxicosis	Use oral decongestants with caution in patients with heart disease **Oral H_1-antihistamine–decongestant combination** products may be more effective than either product alone but side effects are combined

Table 17. Continued

Name and also known as	Generic name	Mechanism of action	Side effects	Comments
Intranasal decongestants	Oxymethazoline Xylomethazoline Others	Sympathomimetic drugs Relieve symptoms of nasal congestion	Same side effects as oral decongestants but less intense **Rhinitis medicamentosa** is a rebound phenomenon occurring with prolonged use (over 10 days)	Act more rapidly and more effectively than oral decongestants Limit duration of treatment to <10 days to avoid rhinitis medicamentosa
Oral/IM glucocorticosteroids	Dexamethasone Hydrocortisone Methylpredisolone Prednisolone Prednisone Triamcinolone	Potently reduce nasal inflammation Reduce nasal hyperreactivity	Systemic side effects common in particular for IM drugs Depot injections may cause local tissue atrophy	When possible, intranasal glucocorticosteroids should replace oral or IM drugs However, a short course of oral glucocorticosteroids may be needed if moderate/severe symptoms
Intranasal anticholinergics	Ipratropium (1535–1537)	Anticholinergics block almost exclusively rhinorrhoea	Minor local side effects Almost no systemic anticholinergic activity	Effective on allergic and nonallergic patients with rhinorrhoea

* Removed from most markets due to side effects.

7.2.1. Routes of administration. Medications used for rhinitis are administered intranasally or orally in the majority of cases. Intranasal medications offer several advantages because high concentrations can be delivered directly into the nose, avoiding or minimizing systemic effects. However, problems are encountered with intranasal medications. Many patients with allergic rhinitis also have conjunctivitis and/or asthma, and medications need to be administered to various target organs. The intranasal distribution of medications is not optimal in many patients. In exceptional circumstances, glucocorticosteroids may be administered intramuscularly because of their unfavorable efficacy/safety ratio.

7.2.1.1. Advantages of intranasal administration

- High concentrations can be delivered directly into the target organ avoiding or minimizing systemic effects.
- Some of the drugs (e.g. cromones) used for the treatment of rhinitis should be administered only via the intranasal route as they are not adequately absorbed when given orally.
- Some drugs have systemic effects when administered orally (e.g. glucocorticosteroids and atropine derivatives).
- The onset of action of an intranasal drug is usually faster than that of an oral drug (e.g. vasoconstrictors and possibly H_1-antihistamines).

7.2.1.2. Problems of intranasal administration

- Some patients experience side effects in the form of crusting and bleeding.
- Many patients with allergic rhinitis present also with conjunctivitis and/or asthma. Intranasal glucocorticosteroids were shown to be effective in allergic conjunctivitis (1449).
- Other local side effects are medication dependent. The prolonged use of an intranasal vasoconstrictor results in the risk of developing *rhinitis medicamentosa* (160). The use of intranasal ipratropium bromide can cause an unpleasant feeling of nasal dryness and also produce blood-tinged mucus. Intranasal glucocorticosteroids can induce mild local side effects, in particular minimal nasal bleeding.
- Intranasal medication cannot be given when the nose is completely blocked.
- Patient compliance may be greater with oral than with topical drugs, especially if multiple target organs are to be treated. The education of the advantages of topical treatment would probably improve compliance.

7.2.2. Oral H_1-antihistamines. H_1-blockers or H_1-antihistamines are medications that block histamine at the H_1-receptor level (neutral antagonists or inverse agonists; 1538). Some also possess additional antiallergic properties (1539). Over the past 20 years, pharmacologic research has produced compounds with a minimal sedative effect and impairment: the so-called second-generation H_1-antihistamines, as opposed to the first-generation H_1-antihistamines (1539). The term 'third'-generation should be reserved for an H_1-antihistamine with novel properties (1540). No drug has met these properties to date.

Oral H_1-antihistamines are effective against symptoms mediated by histamine (rhinorrhoea, sneezing, nasal

itching and eye symptoms) but are less effective on nasal congestion (1229). Their clinical effect in trials of perennial rhinitis lasting 4 weeks and over is usually small. Oral H_1-antihistamines improve the patient's QOL (1066, 1077, 1479). One double-blind, placebo-controlled long-term trial found that levocetirizine was cost-effective in the treatment of PER (1066, 1115).

First-generation oral H_1-antihistamines possess significant side effects due to their sedative and anticholinergic properties. Newer antihistamines induce no (1461, 1468, 1541–1543) or little sedation or impairment (1066, 1544). They are not anticholinergic. Some antiallergic effects have been described (1545, 1546) but their exact clinical relevance is still unclear. Long-term treatment (years) with oral H_1-antihistamines is safe. Some, but not all, oral H_1-antihistamines undergo hepatic metabolism via the cytochrome P450 system and are prone to drug interactions (1547). Although cardiotoxicity is not a class effect (1548), major concerns have existed about the arrhythmogenic action of terfenadine, astemizole and high doses of diphenhydramine which have rarely been associated with fatalities.

Oral H_1-antihistamines have been shown to be safe and effective in children (1108).

Oral H_1-antihistamines have also been approved for young children (1549). Cetirizine, when compared with placebo, delayed or in some cases prevented the development of asthma in a subgroup of infants with atopic dermatitis sensitized to grass pollen and, to a lesser extent, HDM (1550). Further studies are required to substantiate this finding and should focus specifically on sensitized groups.

Several properties should be met by oral H_1-antihistamines (Table 18; 1551).

Table 18 Requirements for oral H_1-antihistamines

Pharmacologic properties
- Potent and selective H_1-receptor blockage.
- Additive anti-allergic activities.
- No clinically relevant pharmacokinetic interference by foods, medications or intestinal transport proteins.
- No known interaction with cytochrome P4503A (CYP3A).
- No known interaction with disease to avoid toxic reactions.

Efficacy
- Effective in the treatment of IAR and PER as defined in the ARIA document
- Effective for all nasal symptoms including nasal obstruction
- Improvement of eye symptoms
- If a claim for asthma is made:
  1 Improvement of asthma symptoms (short-term studies).
  2 Reduction of asthma exacerbations (long-term studies).
  3 Improvement of the pulmonary function tests, even though FEV_1 and peak-flow rates are usually not altered in pollen-induced bronchial symptoms.
- If a claim for a preventive effect is proposed, appropriate trials should be conducted.
- Studies should be carried out on young children and elderly patients to assess efficacy.

Side effects
- No sedation, no cognitive or psychomotor impairment.
- No anti-cholinergic effects.
- No weight gain.
- No cardiac side-effects.
- Possible use in pregnancy and breast feeding.
- Studies should be carried out on young children and elderly patients to assess safety.
- Prospective post marketing safety analyses should be conducted.

Pharmacodynamics
- Rapid onset of action.
- Long duration of action - persistence of clinical effects at the end of the 24-h dosing period, enabling once-daily administrations.
- No likelihood of development of tolerance (tachyphylaxis).

Although first-generation oral H_1-antihistamines are effective, they cannot be recommended when second-generation drugs are available because of their sedative and anticholinergic effects (1552, 1553). Moreover, it has been found that first-generation oral H_1-antihistamines are not cost-effective because of the cost of associated sedation (1145). Only safe second-generation antihistamines should be prescribed because of their favorable efficacy/safety ratio.

As a result of the over-the-counter (OTC) introduction of loratadine in the USA, health plans have attempted to determine the best policy to incorporate this change within their existing drug benefit structure for second-generation H_1-antihistamines (1144). These important changes need to be taken into consideration for optimal cost-effectiveness. The doubling of co-payments was associated with reductions in the use of eight therapeutic classes. The largest decreases occurred for NSAIDs (45%) and antihistamines (44%) (1554).

7.2.3. Topical H_1-antihistamines. Intranasal H_1-antihistamines are effective at the site of their administration in reducing itching, sneezing, runny nose and nasal congestion (1487, 1489, 1492). Given ocularly, they are effective in allergic eye symptoms (1555, 1556). They can be effective within 20 min of administration. Topical H_1-antihistamines require twice-a-day dosing. One formulation of olopatadine is OD for the treatment of allergic conjunctivitis. In general, topical H_1-antihistamines are well tolerated. Use at high dosages is only approved in some countries. A high dose of azelastine may be more effective than oral H_1-antihistamines (1489, 1557), but it produces side effects such as mild somnolence or bad taste in certain patients. Intranasal glucocorticosteroids are significantly more effective than oral or topical

H_1-antihistamines for the treatment of allergic rhinitis and, in particular, for nasal congestion. Intranasal H_1-antihistamines do not appear to improve ocular symptoms (1558).

7.2.4. Intranasal glucocorticosteroids. Intranasal glucocorticosteroids are the most efficacious medication available for the treatment of allergic and nonallergic rhinitis (1449, 1558). The rationale for using intranasal glucocorticosteroids in the treatment of allergic rhinitis is that high drug concentrations can be achieved at receptor sites in the nasal mucosa with a minimal risk of systemic adverse effects. These medications are effective in improving all symptoms of allergic rhinitis as well as ocular symptoms (1559–1561). If nasal congestion is present or symptoms are frequent, an intranasal glucocorticosteroid is the most appropriate first-line treatment as it is more effective than any other treatment (1562, 1563).

Due to their mechanism of action, efficacy appears after 7–8 h of dosing (1564), but maximum efficacy may require up to 2 weeks. However, the onset of action of intranasal glucocorticosteroids may be shorter than previously thought, and some patients benefit within the first 2 h (1325). Fluticasone propionate aqueous nasal spray improves the nasal symptoms of seasonal allergic rhinitis when used as needed (PRN; 1565, 1566).

Intranasal glucocorticosteroids are well tolerated, and adverse effects are few in number, mild in severity and have the same incidence as placebo (1567–1572). However, there are differences in safety between molecules, those with low bioavailability being the best tolerated (1573, 1574). The current intranasal preparations are well tolerated and can be used on a long-term basis without atrophy of the mucosa (814, 1508). Evidence shows that the long-term use of intranasal glucocorticosteroids is free of the concerns associated with the long-term use of oral glucocorticosteroids. Growth has been a concern in children treated with inhaled glucocorticosteroids. The rate of growth was slightly reduced in children regularly treated with intranasal beclomethasone over 1 year (1575). However, no growth retardation has been observed in 1-year follow-up studies of children treated with fluticasone propionate (1576) or mometasone furoate (1577–1579). Moreover, a pharmacokinetic/pharmacodynamic model of the relationship between systemic corticosteroid exposure and growth velocity has been proposed and may be useful for the development of future local glucocorticosteroids (1578, 1579).

Several properties should be met by intranasal glucocorticosteroids (Table 19; 1551).

Table 19 Requirements for intranasal glucocorticosteroids

Pharmacologic properties
- Potent action on transcription factors.
- Non genomic effects.
- First-pass nsk hepatic metabolism.

Efficacy
- Effective in the treatment of IAR and PER as defined in the ARIA document.
- Effective for all nasal symptoms.
- Improvement of eye symptoms.
- If a claim for asthma is proposed:
  1 improvement of asthma symptoms (short-term studies);
  2 reduction of asthma exacerbations (long-term studies) and
  3 an improvement of the pulmonary function tests, even though FEV_1 and nsk peak-flow rates are usually not altered in pollen-induced bronchial symptoms.
- If a claim for nasal polyposis or sinusitis is proposed, the adequate appropriate trials should be conducted.
- If a claim for a preventive effect is proposed, appropriate trials should be conducted.

Side effects
- Minimal local side-effects.
- No HPA nsk axis effects, especially in children and in association with the inhaled (intra-bronchial) form.
- No long-term effect on growth in children.
- Possible use in pregnancy.

Pharmacodynamics
- Assessment of the onset of action.
- Long duration of action, at least 24 h, ability to be administered once a day.
- If a claim for PRN use is proposed, additional appropriate trials should be conducted.

The most effective drugs, e.g. intranasal glucocorticosteroids, are cost-effective when compared to less effective treatments, e.g. intranasal cromoglycate (1142). Comparisons between two intranasal glucocorticosteroids are difficult because drug pricing differs between countries (1143).

Intranasal glucocorticosteroids are also available OTC in many countries (1580) but this raises some concerns (1581).

7.2.5. Antileukotrienes. Several pivotal studies have been carried out on seasonal allergic rhinitis comparing montelukast and placebo. In some studies, the combination of montelukast–loratadine was also used (1521, 1523, 1582–1584). It was consistently found that montelukast was more effective than placebo for all nasal and ocular symptoms and that there was no significant difference between montelukast and loratadine, even for nasal obstruction. Moreover, in contradistinction with the first study (1585), the combination montelukast–

loratadine did not provide any additive beneficial effect over the two drugs alone. The combined montelukast and cetirizine treatment, when started 6 weeks before the pollen season, was effective in preventing allergic rhinitis symptoms and reduced allergic inflammation in the nasal mucosa during natural allergen exposure (1586). Montelukast is equally effective in patients exposed to low and high pollen counts (1523). In one study of perennial rhinitis, montelukast was found to be superior to placebo (1522), but in another study its effects were not superior to placebo and were similar to cetirizine after 1 month of treatment (1587).

In studies carried out on patients with seasonal allergic rhinitis and asthma, montelukast was found to improve nasal and bronchial symptoms (1588, 1589). The use of ß-agonists (puffs/day) was also reduced with montelukast.

Leukotriene receptor antagonists are more effective than placebo, equivalent to oral H_1-antihistamines and inferior to intranasal glucocorticosteroids for treating seasonal allergic rhinitis (1590–1593).

7.2.6. Combination therapy with intranasal glucocorticosteroids. Combination between drugs has been tested, but insufficient data are available to make a recommendation concerning the combined use of oral H_1-antihistamines and intranasal glucocorticosteroids (1099, 1594, 1595). The combination of oral H_1-antihistamines and leukotriene receptor antagonists does not increase the efficacy of any single drug and is less effective than intranasal corticosteroids (1594, 1596, 1597). The combination of ipratropium with beclomethasone dipropionate is more effective than either active agent alone in the treatment of rhinorrhoea (1598).

7.2.7. Cromones. Cromoglycate and nedocromil are available as intranasal or ocular preparations. They are modestly effective in nasal symptoms (1524, 1527, 1599) and effective in ocular symptoms (1600, 1601). They are particularly safe (1).

7.2.8. Decongestants. In the treatment of nasal obstruction, in both allergic and nonallergic rhinitis, intranasal decongestants are effective in the short term (1602, 1603). However, they do not improve nasal itching, sneezing or rhinorrhoea. Very few and small-sized RCTs have been carried out in allergic rhinitis (1604, 1605). Moreover, there are some studies that assess nasal airflow resistance (1606). A prolonged use (>10 days) of intranasal vasoconstrictors may lead to tachyphylaxis, a rebound swelling of the nasal mucosa, and to 'drug-induced rhinitis' (*rhinitis medicamentosa*; 159, 160, 162, 1607, 1608).

Oral vasoconstrictors such as ephedrine, phenylephrine, phenylpropanolamine (banned in some countries including the USA) and especially pseudoephedrine are the most commonly used oral decongestants (1609–1611). Systemic side effects are not rare with oral drugs and include irritability, dizziness, headache, tremor and insomnia as well as tachycardia and hypertension (1). Patients with glaucoma or hyperthyroidism and elderly men with urinary retention due to prostate enlargement are also at risk when using oral sympathomimetic decongestants. Pseudoephedrine was recently banned for Olympic athletes (27).

In many countries, the combination of oral H_1-antihistamines and decongestants represents a large market share (1612–1615). The objectives of these combinations are to improve nasal obstruction which shows little change using oral H_1-antihistamines. As pseudoephedrine is used, the combination bears all the side effects of the vasoconstrictor, and food intake may alter the pharmacokinetics (1616). There are many OTC drugs combining sedative oral antihistamines with decongestants. This combination is not recommended because of the side effects of both components, and in particular sedation.

The combination of ibuprofen and pseudoephedrine was found to be effective in reducing the symptoms of allergic rhinitis (1617).

7.2.9. Anticholinergic agents. Double-blind, placebo-controlled studies have shown that ipratropium bromide is effective in controlling watery nasal discharge, but that it does not affect sneezing or nasal obstruction in perennial allergic and nonallergic (vasomotor) rhinitis (1618–1620). Topical side effects, due to the anticholinergic action, are uncommon and obviously dose-dependent in their severity (1).

7.2.10. Systemic glucocorticosteroids. In rare cases, patients with severe symptoms who do not respond to other drugs or those who are intolerant to intranasal drugs may need to be treated with systemic glucocorticosteroids (e.g. prednisolone, starting dose 20–40 mg/day) for a short period of time (1552). There is a lack of comparative studies on the preferred dose, the route of administration and the dose–response relationship.

Glucocorticosteroids can also be given orally or as a depot-injection (e.g. methylprednisolone 40–80 mg per injection; 1621).

The long-term use (a few weeks) of oral drugs and any use of intramuscular glucocorticosteroids bear the well-recognized risks of systemic glucocorticosteroids. Intramuscular drugs should be avoided (1622).

7.2.11. Other medications. The nonsteroidal anti-NSAID ketorolac is modestly effective when used in ophthalmic preparations (1623).

7.3. Allergen-specific immunotherapy: therapeutic vaccines for allergic diseases

Specific immunotherapy

- Allergen-specific immunotherapy was traditionally administered by the subcutaneous route but local routes are now available.
- Specific immunotherapy needs a precise diagnosis of IgE-mediated allergy.
- Subcutaneous immunotherapy is effective in adults and children for pollen and mite allergy, but it is burdened by the risks of side effects. These reactions may be life-threatening.
- Sublingual immunotherapy is recommended for the treatment of pollen allergy in adults.
- Sublingual immunotherapy may be used for the treatment of patients with mite allergy.
- Intranasal immunotherapy may be used for the treatment of patients with pollen allergy.
- Allergen-specific immunotherapy may alter the natural course of allergic diseases.
- Subcutaneous immunotherapy appears to be effective several years after its cessation.
- Immunotherapy appears to reduce the development of new sensitizations.
- Administered to patients with rhinitis, immunotherapy appears to reduce the development of asthma (secondary prevention of asthma).

Allergen-specific immunotherapy is the practice of administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with the subsequent exposure to the causative allergen. However, there are registered SLIT products which do not require up-dosing. Allergen immunotherapy was introduced in 1911 by Noon and Freeman to treat 'pollinosis' or allergic rhinitis (1624). There is sound evidence that immunotherapy using inhalant allergens is clinically effective in the treatment of allergic rhinitis and asthma (1193). It induces clinical and immunologic tolerance, has long-term efficacy and may prevent the progression of allergic disease. Allergen-specific immunotherapy also improves the QOL of allergic patients (1625, 1626).

Several guidelines and indications for specific immunotherapy with inhalant allergens have been published over the past years by WHO (1193, 1627), the EAACI (1625, 1628–1630), the International Consensus Report on Asthma (1631), the Global Strategy for Asthma Management and Prevention (1140), the International Consensus Report on Rhinitis (9), the British Society for Allergy and Clinical Immunology (1632), the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology (1633), The World Allergy Organization (1634), the British Thoracic Society and ARIA. These reports provide guidelines for a better understanding of the use of allergen-specific immunotherapy.

7.3.1. Allergen standardization. The quality of the allergen vaccine is critical for both diagnosis and treatment. Where possible, standardized vaccines of known potency and shelf life should be used (1635). The most common vaccines used in clinical allergy practice are now available as standardized products (1635) or are pending standardization. It is likely that in the near futures, recombinant allergens will provide standards for allergen analysis and, in consequence, new diagnostic and therapeutic products will be developed (28, 1625).

Allergen vaccines are labeled in units of biological potency based on skin tests. Methods differ in Europe (1636) and in the USA (1637). Each manufacturer defines specific units and concentrations and a whole range of noninterrelated names for specific units currently appear on the labels of marketed products (1638).

- IU (international unit)
- HEP (histamine equivalent prick; 1636)
- AU (allergy unit)
- BAU (biological allergy unit; 1639)
- BU (biological unit)
- IR (index of reactivity)
- TU (therapeutic units), etc.

However, even when the same methodology is used (e.g. Nordic Guidelines) (1636), extracts from different manufacturers labeled with the same units may not be identical in potency, due to differences in the sensitivity of the selected patient population, the relatively small number of patients tested and the different methodologies employed (1625).

The measurement of major allergens for standardization is now a realistic and desirable goal which should be encouraged (1193, 1640). It is recommended that in the future, allergen manufacturers should state the content of representative major allergens in their products in mass units (μg/ml), although comparison between different manufacturers' labeling may not be possible because of differences in assays and methodologies for measurement of the major allergens (28, 1625).

In the European Pharmacopeia, allergen preparations for specific immunotherapy may be (1635):

- unmodified vaccines;
- vaccines modified chemically;

- vaccines modified by adsorption onto different carriers (so-called depot-vaccines);
- modified and depot vaccines developed to make specific immunotherapy more effective and reduce the risks of side effects and
- recombinant allergens.

Allergen vaccines should be distributed, provided their potency, composition and stability have been documented, as follows:

- vaccines from a single source material;
- mixtures of related, cross-reacting allergen vaccines such as grass-pollen vaccines, deciduous-tree pollen vaccines, related ragweed pollen vaccines and related mite vaccines or
- mixtures of other allergen vaccines provided that stability data (1641) and data on clinical efficacy are available. Where mixtures are marketed, the relative amounts of each component of the mixture should be indicated.

7.3.2. *Subcutaneous immunotherapy*

7.3.2.1. Efficacy. The clinical efficacy of SCIT is well established for both rhinitis and asthma, and meta-analyses of its efficacy on asthma (1642, 1643) and rhinitis (1644) are available.

Subcutaneous immunotherapy raises contrasting efficacy and safety issues as does immunotherapy dosing. Low-dose specific immunotherapy is ineffective (1645–1647) and high doses of allergen vaccines may induce a high and unacceptable rate of systemic reactions (1647). Thus, optimal doses using vaccines labeled either in biological units or in mass of major allergens have been proposed (1193). The optimal dose is defined as the dose of allergen vaccine inducing a clinically relevant effect in the majority of patients without causing unacceptable side effects (1648). Doses of 5–20 μg of the major allergen per injection are optimal doses for most allergen vaccines (for review see Refs 1, 1193, 1649).

Since the publication of the ARIA workshop report, several studies have confirmed these findings. Clinical efficacy (reduction of symptoms and/or need for medications) has been confirmed with grass (1102, 1104, 1650–1655), birch (1650, 1651, 1656–1659), ragweed (1660), Russian thistle (1661), *Parietaria* pollen (1662, 1663), mites (1664–1669) and cat (1670). It should be noted that three of the studies (1104, 1660, 1670) clearly demonstrated that the clinical effect is dose dependent. One study showed that recombinant grass pollen vaccines were effective on rhinitis symptoms (1671). Quality of life was improved in patients receiving specific immunotherapy (1104, 1653). In asthma and rhinitis, allergen vaccines are effective for birch and Betulaceae, grass, Cupressaceae, cypress, olive, *Parietaria*, ragweed pollens, cat, HDM and *Alternaria* (1625).

The duration of immunotherapy usually needs to be of 3 years to show long-term efficacy after its cessation (1672–1674).

New forms of ultra-rapid subcutaneous immunotherapy using monophosphoryl lipid A have recently been tested and appear to be promising (1675, 1676).

CpG-adjuved vaccines are also being tested but more data are needed to define their efficacy and safety (1677).

7.3.2.2. Safety. Subcutaneous specific immunotherapy is burdened with a risk of inducing systemic side effects. When treating rhinitis patients, the risk of serious anaphylactic reactions is rather limited compared to when treating asthma patients (1178, 1193, 1649, 1678). In many of the recently published studies, systemic side effects were still noticed using standardized extracts (1104), allergoids (1653) or recombinant allergens (1671). Doses of 5–20 μg of the major allergens are optimal doses for most allergen vaccines (1193) but some patients may experience systemic side effects with these doses (1104).

More postmarketing surveillance studies need to be provided.

Systemic reactions are categorized into immediate systemic reactions (occurring within 30 min) and late systemic reactions (onset > 30 min after injection). A new grading system based on the rate of onset and severity is recommended in Table 20.

Table 20. Classification of systemic reactions induced by immunotherapy [from Ref. (1625)]

0: No symptoms or nonimmunotherapy-related symptoms
I: Mild systemic reactions
Symptoms: Localized urticaria, rhinitis or mild asthma (PF < 20% decrease from baseline)
II: Moderate systemic reactions
Symptoms: Slow onset (>15 min) of generalized urticaria and/or moderate asthma (PF < 40% decrease from baseline)
III: Severe (nonlife-threatening) systemic reactions
Symptoms: Rapid onset (<15 min) of generalized urticaria, angioedema or severe asthma (PF > 40% decrease from baseline)
IV: Anaphylactic shock
Symptoms: Immediate evoked reaction of itching, flushing, erythema, generalized urticaria, stridor (angioedema), immediate asthma, hypotension, etc.

Oral H_1-antihistamine pretreatment during the induction phase has shown to reduce the frequency and severity of systemic side effects [(1679) category of Evidence B, Shekelle et al. (12)].

7.3.2.3. Indications. Double-blind, placebo-controlled studies have confirmed the efficacy of subcutaneous immunotherapy. Clinical efficacy does not necessarily mean clinical indication, especially as controlled trials of immunotherapy are optimally designed and may not always be applicable to daily medical practice. Safe and

effective pharmacologic treatment is also available for the treatment of allergic diseases. Thus, before starting immunotherapy, it is essential to appreciate the respective value of pharmacotherapy and immunotherapy (Table 21).

Table 21. Considerations for initiating immunotherapy [from the WHO Position Paper on Allergen Vaccines (1193) and ARIA (1649)]

1. Presence of a demonstrated IgE-mediated disease
Positive skin tests and/or serum-specific IgE
2. Documentation that specific sensitivity is involved in symptoms
Exposure to the allergen(s) determined by allergy testing related to appearance of symptoms
If required allergen challenge with the relevant allergen(s)
3. Characterization of other triggers that may be involved in symptoms
4. Severity and duration of symptoms
Subjective symptoms
Objective parameters, e.g. work loss, school absenteeism
Pulmonary function (essential in asthmatics): exclude patients with severe asthma
Monitoring of the pulmonary function by peak flow
5. Response of symptoms to pharmacotherapy
6. Availability of standardized or high-quality vaccines
7. Contraindications
Treatment with ß-blockers
Other immunologic disease
Inability of patients to comply
Starting immunotherapy with inhalant allergens during known pregnancy
8. Sociological factors
Cost
Occupation of candidate
9. Objective evidence of efficacy of immunotherapy for the selected patient (availability of randomized-controlled studies)

The indications for subcutaneous immunotherapy are similar to those published in 1998 (1193) and 2001 (1649) (Table 22). Indications and contraindications for allergen-specific subcutaneous immunotherapy are the same for children over the age of 5 years as for adults (28, 1625).

Table 22. Indications for subcutaneous immunotherapy

Patients with symptoms induced predominantly by allergen exposure
Patients with a prolonged season or with symptoms induced by succeeding pollen seasons
Patients with rhinitis and symptoms from the lower airways during peak allergen exposure
Patients in whom antihistamines and moderate dose topical glucocorticoids insufficiently control symptoms
Patients who do not want to be on constant or long-term pharmacotherapy
Patients in whom pharmacotherapy induces undesirable side effects

The practical aspects of subcutaneous immunotherapy have recently been published (1625). Doctors, nurses and healthcare personnel must be trained and regularly updated on subcutaneous allergen-specific immunotherapy including the observation and rescue treatment of systemic anaphylactic reactions. Adrenaline should be readily available.

The economic evaluation of specific immunotherapy *vs* symptomatic treatment of allergic rhinitis was modelized in Germany and France (1146, 1680) and it was found to be cost effective due to the long-term effects of immunotherapy.

7.3.2.4. Natural course of allergic disease. Subcutaneous immunotherapy alters the natural course of allergic diseases. Long-term efficacy of specific immunotherapy persists after it has been stopped (1672, 1673, 1681–1686). Subcutaneous immunotherapy in monosensitized children prevents the development of new sensitizations (1687) and may prevent the development of asthma in patients with rhinitis (1688, 1689). The category of evidence for long-term efficacy and preventive capacity is B (1625).

7.3.3. Sublingual immunotherapy. Sublingual immunotherapy is currently marketed in several European countries and has gained wide acceptance (1690–1692). It is also available in other countries (e.g. Argentina, Brazil, the Gulf States and South Africa). Most extracts are standardized either biologically or immunologically and for most preparations the microgram content of the major allergen(s) is also available. It can be administered using drops or tablets.

7.3.3.1. Efficacy. Sublingual immunotherapy has been controversial for many years and this form of therapy has gained little acceptance in the USA. It was proposed to be ineffective (1693–1695), of concern (1696) or possibly effective but with many unanswered questions (1697). Wilson et al. (1698) published a Cochrane Collaboration meta-analysis of SLIT in rhinitis and proposed that it was safe and effective. The Cochrane meta-analysis (1699) was followed by several studies which accorded with the results of the review (1103, 1700–1711). Moreover, pivotal trials have been carried out and the results on over 600 patients showed convincingly that in grass pollen allergy, SLIT is safe and effective using tablets (1103, 1712). Quality of life was improved in patients receiving SLIT (1713). Sublingual immunotherapy is effective for rhinitis and asthma induced by birch, cypress, grass, olive, *Parietaria* pollens and HDM.

In children, a recent large study did not find any effect, but this study may have been negative due to the relatively low dose of allergen administered. The efficacy of such a schedule has not been confirmed in adults (1714). Another study in mite allergy was carried out on mild–moderate asthmatic children optimally controlled by pharmacologic treatment and HDM avoidance. In this study, SLIT did not provide any additional benefit, despite a significant reduction in the allergic response to HDM (1715). The meta-analysis in children, which showed that the sublingual delivery of an allergen vaccination constituted a safe and effective alternative to the injectable route in reducing allergy respiratory

symptoms and drug intake (1716), should be revised in light of these two trials.

Twenty-five studies involving 1 706 patients were included in a meta-analysis on SLIT in asthma (1717). Immunotherapy was seen to significantly reduce asthma severity when parameter compositions were all analysed by categorical outcomes.

The doses of allergen used in the different studies ranged from 3 to 375 times the cumulative dose of subcutaneous immunotherapy and no definite conclusion was possible (1718). However, large studies with tablets assessed the dose–response of SLIT and it was found that a low dose is ineffective and that a daily dose of around 25 μg of Phl p 5 is required to achieve efficacy. Higher doses are not more effective.

7.3.3.2. Safety. The safety of SLIT has been demonstrated in adults and children by several papers (1719–1722), Phase I trials (1723) and by postmarketing surveillance data (1718, 1724).

Local side effects have been described in clinical trials. These include itching and swelling of the lips and under the tongue. These effects are more common in studies involving high dosage. In general, these effects are well tolerated, requiring no medication or dosage modifications, and often resolve with continued treatment.

In a few clinical trials, systemic reactions such as urticaria and asthma have been observed, all of them self-limiting. Reactions may be dose and allergen dependent (1698). Two recent clinical cases on anaphylactic reactions following SLIT have been published. However, one case was on latex immunotherapy and the other on an ill-defined multi-allergen vaccine (1725, 1726).

Because SLIT is given to the patient at home, the following precautions should be taken (1625):

- the patient (for children, the parents) should be given clear, simple written instructions about what to do in the event of an adverse reaction and
- allergen tablets and drops should be kept in a secure place out of the reach of children.

7.3.3.3. Indications. The indications for SLIT are given in Table 23.

Table 23. Indications for sublingual immunotherapy

High-dose sublingual swallow-specific immunotherapy may be indicated in the following cases:
Carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and mite allergy
Patients insufficiently controlled by conventional pharmacotherapy
Patients who have presented with systemic reactions during injection-specific immunotherapy
Patients showing poor compliance with or refusing injections

7.3.3.4. Sublingual immunotherapy vs subcutaneous immunotherapy. Few studies have compared the two routes of administration. One compared three groups of patients (sublingual, subcutaneous and placebo; 1727) and another used an open design (1728). They did not provide sufficient information due to an insufficient study design. A double-blind, double-dummy study (1729) investigated patients with birch pollen rhinoconjunctivitis. A significant difference between the two active groups and the placebo group in terms of symptom load and drug intake was found. However, the numbers of subjects studied were inadequate to detect a difference between the two active groups, if one existed. More studies with a greater number of patients are needed to evaluate the differences between the routes (1625).

7.3.3.5. Natural course of allergic disease. Sublingual immunotherapy may also impact the natural course of the disease (1730, 1731), but more data are needed for confirmation.

7.4. Anti-IgE

The recombinant, humanized, monoclonal anti-IgE antibody (omalizumab) forms complexes with free IgE, blocking its interaction with mast cells and basophils and lowering free IgE levels in the circulation (1732). In a large pivotal trial, omalizumab decreased serum-free IgE levels and provided clinical benefit in a dose-dependent fashion in patients with seasonal allergic rhinitis (768, 1733). In adults and adolescents, omalizumab was found to decrease all nasal symptoms and to improve RQLQ in patients with rhinitis induced by birch and ragweed pollens as well as in those with sensitization to outdoor allergens (1105, 1734). In patients with asthma and rhinitis, omalizumab improved nasal and bronchial symptoms and reduced unscheduled visits due to asthma (770). The clinical benefit of treatment with omalizumab is associated with an anti-inflammatory effect on cellular markers in blood and nasal tissue (1735, 1736) as well as with a reduction in FcεRI expression and function (1737). Omalizumab inhibits allergen challenge-induced nasal response (1738). It also rapidly decreases nasal allergic response and FcεRI on basophils (1739). The relative efficiency of this treatment compared to H_1-antihistamines and intranasal glucocorticosteroids needs to be established.

Omalizumab was shown in clinical trials and postmarketing surveillance studies to induce rare (0.1% of treated patients) but potentially severe anaphylactic or anaphylactoid reactions (1740, 1741) leading to a change in the labeling. It is recommended that omalizumab should be administered to patients only in a healthcare setting with direct medical supervision for 2 h following the first three injections. Patients also require surveillance for 30 min after further injections.

The cost-effectiveness of anti-IgE has been appreciated for its indication in severe asthma (1742, 1743) but not for rhinitis.

7.4.1. Subcutaneous immunotherapy combined with anti-IgE. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis (1744). The co-seasonal administration of omalizumab after preseasonal specific immunotherapy decreases ocular and nasal symptom scores and rescue medication use in grass-pollen allergic children (1745–1747). This combination might prove useful for the treatment of allergic rhinitis, particularly for polysensitized patients.

7.5. Complementary and alternative medicine

- Many patients who use complementary and alternative medicine appear to be satisfied.
- Evidence-based recommendations are difficult to propose for most complementary and alternative medicine interventions because of methodological problems.
- There is no evidence for the efficacy of most complementary and alternative medicines on allergic rhinitis and asthma.
- The safety of phytotherapy raises concerns.

Complementary/alternative medicines are extensively used in the treatment of allergic rhinitis and asthma (266), but evidence-based recommendations are difficult to propose due to methodological problems in many trials (e.g. not randomized, not controlled, not blinded and with no quantitative measurement; 25, 1748–1751). CAM is widely practised and many patients who use this treatment appear to be satisfied. From a scientific viewpoint, there is no definitive or convincing proof of efficacy for most CAMs in rhinitis or asthma.

Considering the RCTs, there is no clear evidence of the efficacy of acupuncture in rhinitis and asthma.

Some positive results have been described in rhinitis using homeopathy in good quality trials, but an equal number of negative studies counterbalance the positive ones (25). It is therefore impossible to provide evidence-based recommendations for the use of homeopathy in the treatment of allergic rhinitis, and further RCTs are needed.

Some herbal remedies have proved effective in the treatment of rhinitis (1076, 1752, 1753), but there are too few studies to make any firm recommendations. There are also safety and drug interaction concerns associated with these remedies. In fact, herbal remedies are not usually sufficiently standardized and can also contain harmful substances (1754–1756), such as the ephedrine-containing remedies that have been banned in the USA (1757). A mandatory prerequisite for evaluating herbal remedies/mixtures is that the method of preparation, doses, components and active ingredients should be clearly defined, according to the WHO guidelines (1758, 1759).

The therapeutic efficacy of CAM treatments is not supported by currently-available evidence (25). More data from randomized, double-blind, placebo-controlled trials are required. In addition, CAMs may not be devoid of side effects and some of these may interact with other medications (1754, 1756).

7.6. Other treatments

Saline douche is a simple and inexpensive treatment which was shown to bear some efficacy (228, 1760–1762).

Physico-chemical approaches have been proposed. Rhinophototherapy is effective (1763), but more data using simpler equipment are needed. Nasal filters (1764) or pollen-blocker creams (1765) during natural exposure to ragweed and grass pollen can reduce nasal symptoms. An inert cellulose powder has been on sale in the UK since 1994 as a remedy for hay fever and was found to reduce symptoms of pollen rhinitis (1766). In Japan, it is generic to wear a facemask and eyeglasses to prevent pollen inhalation. These masks are effective only if there is no strong wind or outside of the peak pollen season (1767).

Probiotics may influence symptoms of allergic diseases, but more data on large randomized trials are needed (1768, 1769).

7.7. Surgical treatment of rhinitis

As surgery cannot contribute to the treatment of allergic disease itself, it may only be used in certain precise conditions such as turbinate hypertrophy, cartilaginous or bony obstruction of the nasal airways or secondary and independent sinus disease. In patients who have been suffering from perennial allergic or nonallergic rhinitis for many years, a severe drug-resistant hypertrophy of the inferior turbinates may develop, which leads to constant nasal obstruction and watery secretion due to an increase in glandular structures. Consequently, the surgical reduction of the inferior turbinate body and mucosal surface, which should always be limited as much as necessary, reduces nasal obstruction and secretion (1770). Nowadays, endoscopically-controlled minimal-invasive techniques for the sinuses, but also for the turbinates, have replaced former procedures in most countries, and a range of new tools and instruments have been created to allow for more precise and less traumatic surgery. Laser surgery (1771) may also be used. Vidian neurectomy is not indicated for rhinitis because of side effects (1772) and the availability of medical treatment (1773). The indication for nasal and sinus surgery should always be based on a lack of effect of adequate drug treatment and the functional and clinical relevance of the anatomical variation or disease.

Indications for a surgical intervention are:

- drug-resistant inferior turbinate hypertrophy;
- anatomical variations of the septum with functional relevance;
- anatomical variations of the bony pyramid with functional/aesthetic relevance;
- secondary or independently developing chronic sinusitis (1774, 1775);
- different forms of nasal unilateral polyposis (choanal polyp, solitary polyp and allergic fungal sinusitis) or therapy-resistant bilateral NP (1776, 1777) and
- fungal sinus disease (mycetoma, invasive forms) or other pathologies unrelated to allergy (cerebrospinal fluid leak, inverted papilloma, benign and malignant tumors, Wegener's disease, etc.).

7.8. Practical guidelines for the treatment of allergic rhinitis and co-morbidities

7.8.1. Availability and affordability of the treatment. The guidelines are made on the presumption that the suggested treatments are available and affordable to the patient. WHO has published a list of essential drugs (1778). It is important that all the drugs which are of importance in the treatment of rhinitis should be available worldwide. Moreover, even when patients can receive and afford treatment, there is a considerable under-treatment (1779).

The guidelines do not take into account the costs of the treatment. They are made on the presumption that all treatments are readily available and financially affordable to the patient (on health insurance). However, most patients may need to buy drugs, and cost-effectiveness is therefore of importance.

7.8.2. Recommendations for the management of allergic rhinitis. Depending on the classification of allergic rhinitis (seasonal and perennial or IAR and PER), several algorithm-guided therapeutic schemes can be proposed (1, 9, 21, 59, 1377). However, most guidelines are in general agreement (1552; Table 24) and usually follow a progressive management algorithm (1780). The International Primary Care Airways Group and International Primary Care Respiratory Group (21) guidelines follow the 2001 ARIA guidelines and are not presented in the table. It has been shown that in seasonal allergic rhinitis, guideline-guided treatment is more effective than free treatment choice by general practitioners (1406).

Table 24. Therapeutic schemes of guideline-guided treatment in allergic rhinitis [adapted from Ref. (1552)]

Source of guideline	International Consensus on Rhinitis	Joint Task Force on Practice Parameters for Rhinitis	EAACI consensus on allergic rhinitis	ARIA (2001)	ARIA (2007)
Type of statement	Expert panel	Expert panel	Consensus	Expert panel evidence based	Expert panel evidence-based (GRADE)
Diagnostic testing for IgE antibody (skin test or serum-specific IgE)	Indicated if symptoms persist, or QOL affected or SIT considered	Indicated to confirm allergy cause and to identify allergens to avoid or for SIT	No comment	Indicated to confirm allergy cause	Indicated if symptoms persist and/or are moderate/severe, or QOL affected, or SIT considered
Allergen avoidance	Indicated for all patients	Indicated for all patients	Indicated for all patients	Indicated (evidence D)	Usually not indicated as a public health measure. May be helpful in some highly-selected patients
First-generation oral H_1-blocker	Not recommended	Not recommended	Not recommended	Not recommended because of unfavorable efficacy/safety ratio	Not recommended because of unfavorable efficacy/safety ratio
Second-generation oral H_1-blocker	Mainstay treatment for mild–moderate disease and in combination with intranasal corticosteroid (INCS) for severe disease	First-line therapy and for prophylactic use, but not effective alone for nasal congestion	First-line therapy, but not effective alone for nasal congestion	First-line therapy except for moderate/severe persistent rhinitis, not effective alone for nasal congestion	First-line therapy except for moderate/severe persistent rhinitis (or added to INCS)
Topical H_1-blocker (intranasal or topical conjunctival)	Same as oral	Same as oral	Same as oral	Same as oral, rapidly effective	Same as oral, rapidly effective
ICNS	Primary agents for moderate/severe diseases and for nasal obstruction, but relief is less rapid than H_1-blockers	Especially for moderate/severe disease	First-line treatment for moderate/severe or persistent disease, despite slow onset of action (12 h), effective for nasal congestion, particularly in perennial rhinitis	First-line treatment for moderate/severe disease, particularly in persistent rhinitis, despite slow onset of action (12 h), effective for nasal congestion	First-line treatment for moderate/severe disease, in particular in persistent rhinitis, despite slow onset of action (12 hr), effective for nasal congestion

Table 24. Continued

Source of guideline	International Consensus on Rhinitis	Joint Task Force on Practice Parameters for Rhinitis	EAACI consensus on allergic rhinitis	ARIA (2001)	ARIA (2007)
Antileukotriene	No comment	No comment	No comment	One study only. Indication difficult to delineate	In rhinitis, efficacy similar to oral H_1-blockers. Effective on asthma and rhinitis.
Cromone (intranasal or topical conjunctival)	Safe and effective, but less effective than other medications	Safe and effective in some patients, especially if begun early in season	Safe and effective, but less effective than other medications	Safe and effective, but less effective than other medications	Safe and modestly effective, and less effective than other medications
Decongestant (oral)	Indicated in combination with oral H_1-antihistamines	Indicated in combination with oral H_1-antihistamine to reduce congestion		Indicated in combination with oral H_1-antihistamine to reduce congestion. Safety issues	Indicated in combination with oral H_1-antihistamine to reduce congestion. Safety issues
Depot corticosteroid	Not recommended	Not recommended because of side effects	Not recommended because of side effects	Not recommended because of side effects	Not recommended because of side effects and lack of evidence on efficacy
Intranasal anticholinergic	Indicated to reduce rhinorrhoea not controlled by other medications	Indicated to reduce rhinorrhoea but not effective in other symptoms	Indicated to reduce rhinorrhoea not controlled by other medications	Indicated to reduce rhinorrhoea not controlled by other medications	Indicated to reduce rhinorrhoea not controlled by other medications
Subcutaneous immunotherapy	Indicated if response to primary therapy is poor, if compliance with pharmacotherapy is low, or if complications (asthma) are present	Indicated if symptoms are severe or protracted or if other treatment fails; to prevent progression or development of complicating illnesses	Indicated if only 1 or 2 relevant allergens and pharmacotherapy and avoidance therapy are insufficient; risk of systemic effects	Indicated if only 1 or 2 relevant allergens and pharmacotherapy and avoidance therapy are insufficient; risk of systemic effects	Indicated if only 1 or 2 relevant allergens and pharmacotherapy and avoidance therapy are insufficient; risk of systemic effects
Sublingual immunotherapy	No comment	No comment	Indicated in the same conditions as subcutaneous immunotherapy and for seasonal allergic rhinitis; may be safer than subcutaneous immunotherapy	Indicated in the same conditions as subcutaneous immunotherapy with some reservations; is safer than subcutaneous immunotherapy	Indicated in the same conditions as subcutaneous immunotherapy; is safer than subcutaneous immunotherapy
Referral to allergy or other specialist	Indicated if response to environmental control is poor, if >2 courses a year of oral glucocorticosteroids are required, if complications of rhinitis are chronic or recurrent (e.g. sinusitis, Eustachian tube dysfunction) or if immunotherapy is indicated	Indicated if response to drugs is poor; if immunotherapy is required, if complications of rhinitis are chronic or recurrent (e.g. sinusitis), if systemic glucocorticosteroids are needed to control symptoms, or if symptoms persist for >3 months	No comment	Indicated if symptoms persist for >3 months	Indicated if response to drugs is poor or if symptoms persist for >3 months
Pharmacist assessment	No comment	No comment	No comment	A pharmacist pocket guide has been produced	Pharmacists are part of the management of rhinitis as OTC drugs are common worldwide
Patient's views	No comment	No comment	No comment	Developed with patients' associations	Developed with patient's associations

However, pharmacologic treatment based on guidelines (9) is not effective in all patients (1406). Around one-third of patients with moderate/severe symptoms are uncontrolled despite optimal pharmacologic treatment and some still have severe symptoms, particularly conjunctivitis and nasal obstruction.

7.8.3. ARIA guidelines

7.8.3.1. Methodology for the updated recommendations. Considerable progress has been made in obtaining reliable evidence on the beneficial effects of interventions, but developments in the identification, interpretation and reporting of harmful effects is more challenging (1781). RCTs are insufficient in the assessment of the side effects of treatments, and postmarketing surveillance is required. There is an urgent need to obtain better evidence on the side effects (risks; 1421; Fig. 8).

The recommendations follow criteria which may differ from country to country, and in Europe and at WHO another Shekelle method was commonly used (12; Table 25).

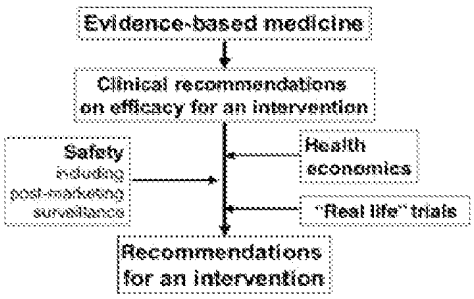

Figure 8. Development of guidelines [from Bousquet et al. (1782)].

Table 25. Shekelle guide for level of evidence [from Shekelle et al. (12)]

Level of evidence
Ia: Meta-analysis of randomized-controlled trials (RCT)
Ib: At least one RCT
IIa: At least one controlled study without randomization
IIb: At least one other type of study
III: Nonexperimental descriptive studies
IV: Expert committee reports or opinions or clinical experience of respected authorities
Strength of recommendation
A: Category I evidence
B: Category II evidence or extrapolated recommendation from category I evidence
C: Category III evidence or extrapolated recommendation from category I or II evidence
D: Category IV evidence or extrapolated recommendation from category I, II or III evidence

However, a number of approaches have been used to grade levels of evidence and the strength of recommendations (1423). The large number of systems for measuring the quality of evidence and recommendations is confusing and all currently-used approaches for grading levels of evidence and the strength of recommendations have important shortcomings (1783). The 'Guidelines for WHO guidelines' recommend using a specific, uniform grading system (1784). The GRADE approach is one of the recommended systems (1423) and is being used increasingly by a number of organizations. The GRADE working group has published the results of its work (22). It classifies recommendations into two levels – strong and weak – and quality of evidence into four levels – high, moderate, low and very low (1423).

It appears that recommendations based on efficacy only are insufficient for classifying clinical practice guidelines, and panels should consider several factors (Table 26). When the benefits of an intervention clearly outweigh its risks and burden, or clearly do not, strong recommendations are warranted.

Table 26. Factors that panels should consider when deciding on strong or weak recommendations [from Guyatt et al. (1422)]

Methodological quality of the evidence supporting estimates of likely benefits, and likely risk, inconvenience and costs
Importance of the outcome that treatment prevents
Magnitude of treatment effect
Risks associated with therapy
Burdens of therapy
Risks of target event
Costs

The 1994 International Consensus for Rhinitis guidelines (9) followed a stepwise approach in the treatment of allergic and nonallergic rhinitis, because this seemed to be the most practical approach **for the general practitioner and for the specialist.**

In 1999, the EAACI proposed new guidelines (59) and, unlike the **1994 guidelines (9)**, not only the mild and moderate cases were considered, but also the severe ones.

In the ARIA guidelines, the suggestions were made by a panel of experts and were based on an extensive review of the literature available up to December 1999 (1). Papers for the review were extracted from Medline using PubMed and Embase. A consensus was reached on all of the material presented in this position paper. The panel recognized that the suggestions put forward were valid for the majority of patients within a particular classification but that individual patient responses to a particular treatment may differ from the suggested therapy. It was assumed that a correct diagnosis was achieved before treatment. The statements of evidence for the development of these guidelines followed WHO rules and were based on Shekelle et al. (12). The statements of evidence for the different treatment options of allergic rhinitis have been examined by the ARIA panel (Table 27).

The ARIA update is also evidence based. However, most trials were carried out before the new classification of allergic rhinitis was made and are reported for seasonal and perennial rhinitis.

Table 27. Level of evidence of different interventions in allergic rhinitis: The level of evidence was produced according to Shekelle et al. (12), adapted from Refs (24–28).

	Seasonal rhinitis		Perennial rhinitis (mostly applies for studies ≤ 4 weeks)*		Persistent rhinitis†
Intervention	Adults	Children	Adults	Children	
H_1-antihistamine					
Oral	A	A	A	A	A
Intranasal	A	A	A	A	No data
Intraocular	A	A	B	B	No data
Glucocorticosteroid					
Intranasal	A	A	A	A	No data
Oral	A	B	B	B	No data
IM	A	B	B	B	No data
Cromones					
Intranasal	A	A	A	B	No data
Intraocular	A	A	B	B	No data
NAAGA (topical)	B	C	C	C	No data
Antileukotriene	A	A over 6 years			No data
Decongestant					
Intranasal	C	C	C	C	No data
Oral	A				No data
Oral + H_1-antihistamine	A	B	B	B	No data
Anticholinergic			A	A	No data
Homeopathy	D	D	D	D	No data
Acupuncture	D	D	D	D	No data
Phytotherapy	B	D	D	D	No data
Other CAM	D	D	D	D	No data
Specific immunotherapy: rhinoconjunctivitis					
Subcutaneous	A	A	A	A	No data
Sublingual‡	A	A	A	A	No data
Intranasal‡	A				No data
Specific immunotherapy: asthma					
Subcutaneous	A	A	A	A	
Sublingual‡	A	A	A	A	
Anti-IgE	A	A over 12 years	A	A over 12 years	No data
Allergen avoidance					
House dust mites	D	D	D	D	No data
Other indoor allergens	D	D	D	D	No data
Total avoidance of occupational agent			A (for asthma)		No data
Partial avoidance of latex			B		No data

* Very few studies longer than 4 weeks.
† Applies to treatments only carried out in studies with persistent rhinitis.
‡ Applies to high-dose treatment.

7.8.3.2. Rationale for updated recommendations. Since the ARIA workshop report, several studies have been undertaken. They can be summarized as follows:

- seasonal and perennial rhinitis is not synonymous with IAR and PER. The ARIA subdivision was found to be closer to the patients than the previous classification. Thus, the categorization of IAR and PER should be maintained;
- however, it is likely, but not demonstrated, that nasal inflammation persists longer in patients with PER than in those with IAR;
- allergen avoidance for the tertiary prevention of allergic rhinitis has not been found to be effective for most indoor allergens. It cannot be proposed as a general measure. However, it is reasonable to avoid direct exposure to pets in allergic subjects. In some patients with a very high allergen load in the home and after environmental counseling, a multifaceted intervention against HDMs might be proposed;
- only one study was published in patients with PER and it was found that levocetirizine reduces symptoms and improves the QOL of patients with moderate/severe disease and
- sublingual immunotherapy is now fully validated, at least in adults.

However, treatment should be tailored according to the severity of the disease, co-morbidities, treatment availability and affordability and patients' preference. Thus, a list of options is indicated in the updated ARIA recommendations. Moreover, labeling variations for

medications exist between countries and should be taken into consideration before prescribing.

7.8.3.3. Updated ARIA recommendations (Fig. 9).

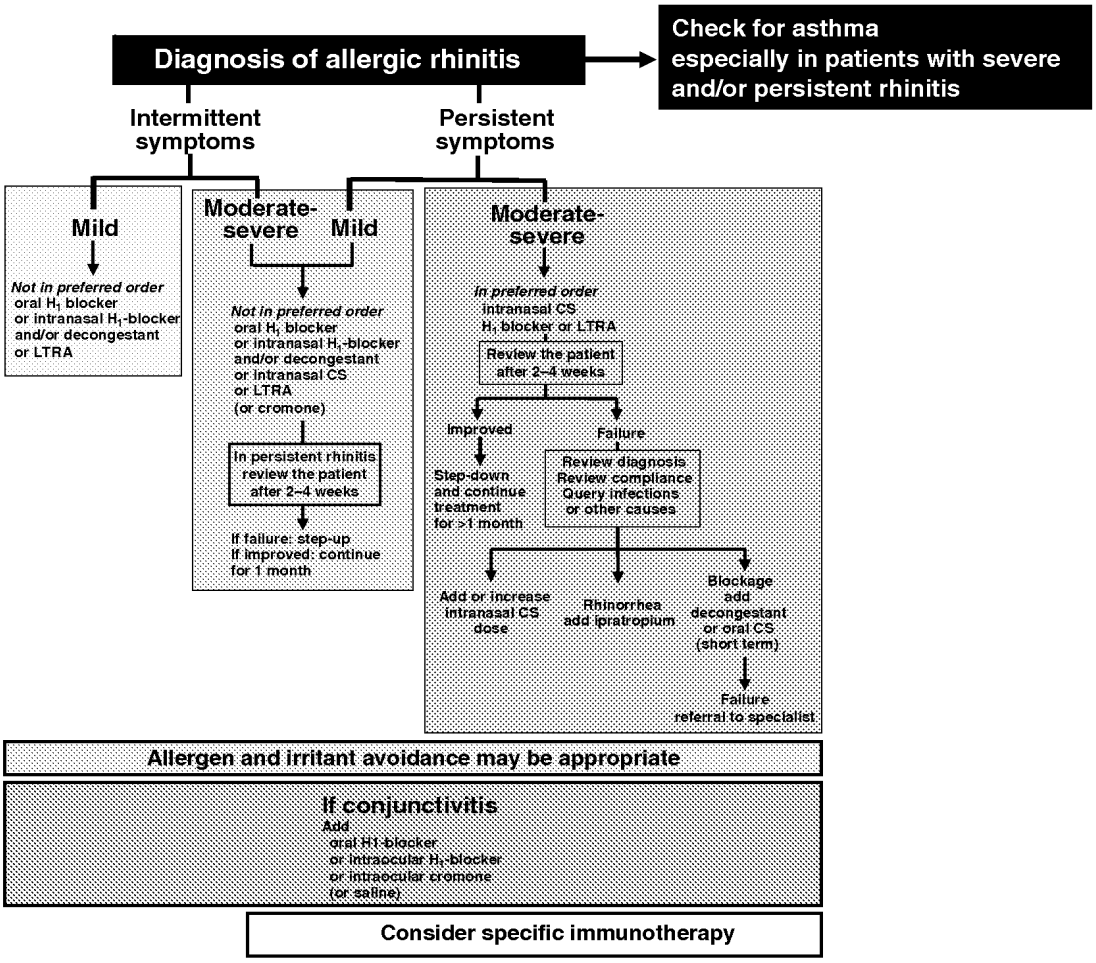

Figure 9. Rhinitis management.

7.8.3.4. Management of rhinitis in developing countries. In developing countries, the management of rhinitis is based on medication affordability and availability (1785) and on cultural differences (1786). The rationale for treatment choice in developing countries is based upon:

- level of efficacy;
- low drug cost affordable for the majority of patients;
- inclusion in the WHO essential list of drugs: only chlorpheniramine and beclomethasone are listed (1778). It is hoped that new drugs will be available on this list when they become affordable for patients in developing countries and
- most chronic diseases are treated for their acute symptoms and no long-term plan is proposed.

In the first ARIA document, it was proposed that specific immunotherapy was contraindicated in low-income countries because the resources allocated to specific immunotherapy might be better allocated to a wider use of generic drugs such as topical glucocorticosteroids (1). In the ARIA update, new recommendations have been proposed (28). Moreover, the diagnosis of allergy in most developing countries is difficult because allergens in the environment are ill-defined and there is a lack of trained specialists, as a result of which appropriate testing cannot be done. In this case, specific immunotherapy should not be performed. The diagnosis of allergy should be determined by trained health professionals when allergens are well defined. Taking these considerations into account, no general rule can be applied to all countries. In countries where there are trained allergists, where relevant local allergens have been identified and high-quality vaccines are available, specific immunotherapy can be performed. If specific immunotherapy is used, its cost-effectiveness at individual level should be evaluated depending on the healthcare priorities, health system and resources of each country. In developing countries, it is recommended that doctors working with specific immunotherapy receive regular updating in the field.

A stepwise medical treatment was proposed in the ARIA workshop report (1):

- mild IAR: oral H_1-antihistamines;
- moderate/severe IAR: intranasal glucocorticosteroids (equivalent beclomethasone 300–400 μg daily) should be prescribed. If needed, after 1 week of treatment, oral H_1-antihistamines and/or oral glucocorticosteroids should be added;
- mild PER: treatment with oral H_1-antihistamines or a low dose of intranasal corticosteroid (equivalent beclomethasone 100–200 μg) should be sufficient and
- moderate/severe PER: a high dose of intranasal glucocorticosteroids (equivalent beclomethasone 300–400 μg) should be prescribed. If symptoms are severe, add oral H_1-antihistamines and/or oral glucocorticosteroids at the beginning of the treatment.

Asthma management for developing countries was developed in a guide proposed by the International Union against Tuberculosis and Lung Diseases (The Union) in 1996 and was revised in 2006 (1787). The affordability of inhaled steroids is usually low in developing countries. If it is affordable for the patient to treat the two manifestations of the disease, it is recommended to add the treatment of allergic rhinitis to the asthma management plan.

7.8.4. Management of allergic rhinitis in the pharmacy. Worldwide, pharmacists receive sophisticated clinical training. Given the well-known and well-publicized recognition of iatrogenic disease, pharmacists' skills represent an enormous potential resource in maximizing the benefits and minimizing the adverse events associated with pharmacotherapy (1788). Pharmaceutical care includes the prevention, treatment or cure of a disease (1789). Interest and expectation that pharmacists provide broader 'pharmaceutical care' services has therefore increased (1790). Pharmaceutical care for the patient is likely to be optimal when there is collaboration between pharmacists, patients and other healthcare professionals,

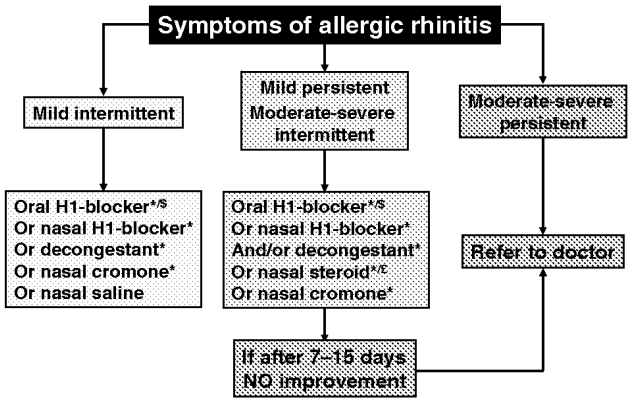

Figure 10. Management of allergic rhinitis in the pharmacy [from Ref. (1154)].

specifically doctors (85). However, there are major differences between countries.

As trusted healthcare professionals in the community, pharmacists are well placed to identify the symptoms of allergic rhinitis and to recommend appropriate treatment by:

- understanding the effect of treatment on rhinitis and co-morbidities;
- determining whether management in the pharmacy is appropriate (Figure 10);
- initiating an appropriate treatment and monitoring plan;
- proposing appropriate preventive measures and
- assessing co-morbidities.

7.8.5. Specific considerations

7.8.5.1. Pediatric aspects. Allergic rhinitis is part of the 'allergic march' during childhood (1426, 1791) but IAR is unusual before 2 years of age. Allergic rhinitis is most prevalent during school-age years.

The principles of treatment for children are the same as for adults, but special care has to be taken to avoid the side effects typical in this age group. A Cochrane meta-analysis was recently published concerning the efficacy of intranasal glucocorticosteroids in children with IAR and PER but the papers analysed may not be totally adequate (1792).

7.8.5.2. Pregnancy. Nasal physiological changes exist during pregnancy (1793). Pregnancy rhinitis is a very common condition. Defined as 'nasal congestion present during pregnancy without other signs of respiratory tract infection, and with no known allergic cause, disappearing completely within 2 weeks after delivery', it strikes one in five pregnant women and can start in almost any gestational week (171).

Rhinitis is often a problem during pregnancy as nasal obstruction may be aggravated by pregnancy itself (168). Caution must be taken when administering any medication during pregnancy, as most medications cross the placenta (1794, 1795). For most drugs, limited studies have been performed only on small groups without long-term analysis (1796, 1797). Moreover, there are differences in regulations between countries and it is advisable to conform to the country's regulations.

Nasal glucocorticosteroids are not very effective in nonallergic pregnant women (1798) but could be used when indicated for other sorts of rhinitis. Nasal decongestants provide good temporary relief, leading to their over-use by pregnant rhinitics (171).

7.8.5.3. Elderly people. With ageing, various physiological changes occur in the connective tissue and vasculature of the nose which may predispose or contribute to chronic rhinitis (1799). Moreover, there are unpredicted

pharmacokinetic changes in the elderly, but there is no clear study for drugs used in allergic rhinitis. Some drugs may induce specific side effects in elderly patients (1800, 1801).

In the elderly, intranasal glucocorticosteroids, at the recommended dose, have not been associated with an increased risk of fractures (1802). The cardiovascular and urinary risks of nasal or oral decongestants should be considered.

Many elderly patients receive numerous treatments for co-morbidities. Some of them such as ß-blockers and ACE inhibitors may induce or aggravate symptoms associated with allergic diseases.

7.8.5.4. Sport and exercise. In the ARIA update, recommendations for athletes address the issue of adapting diagnosis and management to criteria set by the International Olympic Committee (IOC) and regulations adopted by the World Anti-Doping Agency (WADA; 27). The recommendations are given in Table 28.

- either a positive bronchodilator test with an increase in $FEV_1 \geq 12\%$, positive exercise test, a positive eucapnic hyperventilation test or cold air challenge test with a reduction in FEV_1 of $\geq 10\%$
- or a positive methacholine bronchial challenge test with $PC_{20} \leq 4$ mg/ml or $PD_{20} \leq 2$ µmol in steroid-naive athletes (without inhaled steroids for the last 3 months) or in athletes using inhaled steroids with $PC_{20} \leq 6.6$ mg/ml or $PD_{20} \leq 13.6$ µmol.

The WADA prohibited list of drugs in sports is usually updated and changed every year. The IOC regulation may also be changed before the next Olympic Games. Doctors treating athletes should remain updated regarding these regulations.

7.9. Education

Education of the patient and/or the patient's carer on the management of rhinitis is essential. Such education is likely to maximize compliance and optimize treatment outcomes (1804). Patient information, as well as the communication and partnership of the treating healthcare professional and the patient, appears to be of importance. A written self-management and emergency plan is also important in patients with severe disease. However, the benefit of education has never been tested in terms of treatment efficacy, compliance and effectiveness in allergic rhinitis.

The training of healthcare professionals is important but very few studies have been performed. A recent study

Table 28. List of permitted and prohibited antiallergic treatment [from the WADA (1803), International Olympic Committee (http://www.olympic.org/uk/games/torino/atue/index_uk.asp) and Bonini et al. (27)]

Treatment	WADA rules	IOC rules	Notes
Antihistamines	Permitted	Permitted	Second-generation H_1-antihistamines should be preferred to avoid somnolence
Antileukotrienes	Permitted	Permitted	
Oral glucocorticosteroids	Prohibited in competition, require therapeutic use exemption approval	Prohibited in competition, require therapeutic use exemption approval	
Topical glucocorticosteroids	Require an abbreviated therapeutic use exemption approval	Need notification	
Oral $ß_2$-agonists	Prohibited	Prohibited	
Inhaled salbutamol, terbutaline, formoterol, salmeterol	Require an abbreviated therapeutic use exemption approval	Documentation of bronchial hyperresponsiveness, reversibility to inhaled bronchodilators, positive exercise test, eucapnic hyperventilation test or cold air challenge must be documented*	A concentration of salbutamol >1 µg/ml is considered an adverse analytic finding unless proven as due to therapeutic use of inhaled salbutamol
Ephedrine, methylephedrine, pseudoephedrine	Prohibited in competition, pseudoephedrine permitted	Prohibited in competition, pseudoephedrine permitted	Ephedrine and methylephedrine concentration in urine >10 µg/ml represents an adverse analytic finding
Immunotherapy	Permitted	Permitted	Immunotherapy should not be performed before or after physical exercise
Inhaled or nasal ipratropium bromide	Permitted	Permitted	
Disodium cromoglycate	Permitted	Permitted	

A notification for the use of inhaled glucocorticosteroids and an application for the use of inhaled $ß_2$-agonists must be made to the Medical Committee of the International Olympic Commission at the latest 2 weeks before the Olympic Games. For the last Olympic Games in Torino, a website was created where an on-line application could be made (http://www.olympic.org/uk/games/torino/atue/index_uk.asp). To be allowed to use inhaled salbutamol, terbutaline, salmeterol or formoterol, at least one of the following requirements had to be met:

showed that standardized allergy education given to primary healthcare professionals leads to modest improvements in the disease-specific QOL of patients with perennial rhinitis (1805).

8. Health promotion and prevention

Primary and secondary prevention

- Breastfeeding is recommended regardless of the atopic background of the infant.
- Current dietary manipulations of maternal and infant feeding do not have a preventive role for atopic diseases and are not recommended.
- Environmental tobacco smoke should be avoided in pregnant women and children although more data are needed.
- Conflicting data exist concerning the early-life exposure to pets and the development of atopy. No general recommendation can be made.
- House dust mite avoidance in infancy has inconsistent effects on the development of allergy or asthma and cannot be recommended.
- Primary prevention of OAD is recommended.
- Secondary prevention of asthma is still a matter of debate and more data are needed.

Health promotion is the process enabling people to increase control over their health and its determinants. It is a core function of public health and a cornerstone of primary health care (1806). The cost-effectiveness of any program should be carefully evaluated before it is implemented.

There is a general misconception that the same factors involved in the induction of allergy are also likely to incite disease. However, this is not necessarily the case. Thus, strategies for primary prevention or prophylaxis may be very different to those required for the management of established disease. A more complete description of preventive measures is reported in the WHO initiative 'Prevention of allergy and asthma' (1807).

8.1. Primary prevention of atopic diseases

The role of primary prevention of allergic diseases has been a matter of debate for the last 40 years and is not yet resolved (1808). More research is required and longer periods of follow-up are necessary for all current intervention studies aimed at reducing exposure, the onset and duration of intervention and other novel intervention measures in the primary prevention of asthma and allergic diseases in childhood (1809, 1810).

8.1.1. Maternal and infant feeding. Much of the early efforts at allergen avoidance have focused on infant feeding and, in particular, the early avoidance of cows' milk protein and sometimes egg, fish and nuts. Most studies have commenced avoidance in the postnatal period and results have been variable with no clear-cut view emerging.

In 2001, a meta-analysis was carried out concerning breastfeeding and it was found that although some protective effect against atopic dermatitis and/or wheezing existed in studies lasting <4 years, the benefits were less pronounced in studies where participants were followed for a longer period of time (1811). More recent studies (1812–1814) and meta-analyses (1815–1817) have not changed the results of the first one. Moreover, the risk of asthma was found to be enhanced in breastfed children after the age of 6 years in some (1818–1820) but not all prospective studies (1821, 1822). Results from a developing country suggest a protective effect of prolonged breastfeeding on the development of allergic disease, particularly hay fever, in children born to nonallergic parents. This protective effect was not found in children with an allergic predisposition (1823). Breastfeeding is therefore highly recommended for all infants (1824), irrespective of atopic heredity, because its preventive effect on atopy is not demonstrated (1808, 1815). Reasons for these controversies include methodological differences and flaws in the studies performed to date, the immunologic complexity of breast milk itself and, possibly, genetic differences among patients that would affect whether breastfeeding is protective against the development of allergies or is in fact sensitizing (1825–1827).

In high-risk infants who are unable to be completely breastfed, there is evidence that prolonged feeding with a hydrolyzed compared to a cows' milk formula reduces infant and childhood allergy and infant cows' milk allergy (1828). Another Cochrane meta-analysis proposed that feeding with a soya formula cannot be recommended for the prevention of allergy or food intolerance in infants at a high risk of allergy or food intolerance (1829).

Further trials are required to determine whether significant clinical benefits persist beyond 5 years of age and if there is any additional benefit from the use of an extensive compared to a partially-hydrolyzed formula. Incremental costs of the formula and the effect on compliance should be measured.

A panel studied the optimal age for the introduction of solid foods in infants with an atopic risk (1830) and proposed that selected supplemental foods should be introduced after 6 months, dairy products 12 months, hens' eggs 24 months and peanuts, tree nuts, fish and seafood at least 36 months. For all infants, complementary feeding can be introduced from the sixth month, but egg, peanut, tree nut, fish and seafood introduction require caution.

The prescription of an antigen-avoidance diet to a high-risk woman during pregnancy is unlikely to substantially reduce her child's risk of atopic diseases, and such a diet may adversely affect maternal or fetal nutrition or both (1831). The prescription of an antigen-avoidance

diet to a high-risk woman during lactation may reduce her child's risk of developing atopic eczema, but improved trials are needed (1831). Furthermore, there is at least limited evidence that early dietary manipulation may be a risk for impaired growth. Therefore, great caution is required in employing such approaches (1832).

8.1.2. House dust mites. Indoor allergens have a major impact on rhinitis and asthma, and exposure in sensitized subjects can compromise lung function. A reduction in indoor allergen exposure would seem a logical facet to treatment (336, 1426). Methods for reducing mite allergen levels that are effective in the laboratory may not work in the home and may not result in a clinical benefit. Several ongoing studies are investigating the effects of environmental control on the primary prevention of asthma and allergies. Although the results of a pan-European study (1833) of 4 y old children and the Isle of Wight (1834) and Canadian studies (1835) at ages 8 and 7 y provide some encouragement, the preventive effect of the avoidance of HDM allergen alone during pregnancy or after birth is disappointing (1836–1841). It will therefore be some time before a definitive public health message emerges.

8.1.3. Early exposure of pets. Several studies have shown conflicting results on the influence of early-life exposure to indoor allergens and the subsequent development of sensitization and symptoms (249, 1842, 1843). The German Multi-Center Allergy Study (1844, 1845) and the Dutch PIAMA study (1846) reported a dose–response relationship between early cat exposure and sensitization in children. In another study, feather pillow use and the ownership of pets with fur did not increase the risk of developing allergic rhinitis (1847). On the other hand, early exposure to cats or dogs was found to protect against a later allergy development (1848–1851). Another study in the USA showed an inverse U-shape association between cat exposure and sensitization (1852). There are also studies reporting no association between cat allergen exposure and sensitization (1853, 1854). Methodological challenges need to be addressed in these studies. As an example, the inverse association between current pet ownership and sensitization and rhinitis symptoms may be partly due to the removal of pets in families with sensitized and/or symptomatic children (1855). Moreover, other bias may be found because there seems to be a selection of pet exposure based on the parental history of allergy, maternal smoking and socioeconomic factors (1856).

Many children exposed to high levels of Fel d 1 in dust at home produce an IgG and IgG_4 antibody response to Fel d 1 without an IgE antibody (1852). This modified Th2 response is not associated with symptoms and may be regarded as a form of immunologic tolerance (1857).

8.1.4. Occupational agents. Very few surveillance programs have been carried out to assess the efficacy and effectiveness of primary prevention (1436, 1858) and some are subject to criticism. In workers exposed to enzymes, preventive measures have been found to reduce the onset of asthma (1859–1861). The primary prevention of natural rubber latex allergy is still a matter of discussion although widely proposed (1435, 1862). Two meta-analyses were published in 2006. One found that there were no studies of sufficient quality to make any conclusion (137), the second proposed such an intervention (1863). However, it seems justified to propose a reduction of latex levels in healthcare workers. The primary prevention of occupational asthma due to isocyanates is questionable because occupational asthma cases have been reduced in countries where measures are implemented (1864) as well as in those where no surveillance program is applied (1865).

8.1.5. Environmental tobacco smoke. Many children are exposed to tobacco smoking, both before and after birth. Smoking during pregnancy affects fetal lung development especially when there is a family history of asthma and hypertension during pregnancy (1866, 1867) and causes abnormal airway function (1868). Effects of ETS due to parental smoking on wheezing in early childhood have been described in epidemiologic studies (1869–1873) but few have made an effort to discriminate between the effects of prenatal and postnatal exposure. Recent studies suggest that smoke exposure *in utero* may be at least as detrimental to respiratory health in early life as postnatal exposure to ETS (1874). Another study suggested that *in utero* exposure is more important (1875). There is not usually any association between atopy, rhinitis, eczema and parental smoking (1873). Counseling parents to stop smoking still remains an important policy.

8.1.6. Prevention of the development of asthma in rhinitis patients. Allergen vaccination is primarily used to improve symptoms of allergic diseases, but certain data show that allergen vaccination may be preventive. Allergen vaccination in patients with only allergic rhinoconjunctivitis may prevent the onset of asthma (1876). A multicenter Preventive Allergy Treatment (PAT) study started in children aged 7–13 y (1688) showed that the actively-treated children had significantly fewer cases of new onset asthma than the control group after 3 years on allergen immunotherapy. Methacholine bronchial provocation test results improved significantly in the actively-treated group only. The effect persisted for 2 years after the cessation of immunotherapy (1689).

Some SLIT studies have suggested a similar effect (1877) but more data are needed to fully appreciate the exact role of SLIT. However, since SLIT may be started earlier than subcutaneous immunotherapy in infants, it has a potential role for the secondary prevention of allergic diseases.

Pharmacotherapy was tested in infants at a high risk of developing asthma and results are not yet consistent. Ketotifen (1878) and cetirizine (1550, 1879) have been found to reduce wheezing, at least in a subgroup *post hoc* analysis (1879), but the data need confirmation. The first study was

relatively underpowered and the second only found a significant protective effect in the predefined *post hoc* analysis of a nonsignificant primary end point. The EPAC study will be the definitive study and results are pending.

8.1.7. Secondary prevention of new sensitizations. Several longitudinal studies report that allergic sensitization increases with age from childhood to adulthood. House dust mite sensitization and, to a lesser degree, pollen sensitization, seem to play a 'triggering' role in the development of polysensitization, because a high proportion of children originally monosensitized to HDMs or to pollens became polysensitized. Case–control studies have shown that many monosensitized patients treated with subcutaneous immunotherapy do not develop a new sensitization, whereas those who do not receive immunotherapy become polysensitized (1672, 1684, 1880).

9. Links between rhinitis and asthma

The nasal airways and their closely-associated paranasal sinuses are an integral part of the respiratory tract (1, 14, 1881). The nasal and bronchial mucosa present similarities and one of the most important concepts regarding nose–lung interactions is the functional complementarity (14). Most patients with asthma have rhinitis (18) suggesting the concept of 'one airway one disease'. The presence of allergic rhinitis commonly exacerbates asthma, increasing the risk of asthma attacks, emergency visits and hospitalizations for asthma. However, not all patients with rhinitis have asthma and there are differences between rhinitis and asthma (19, 20).

In this section, the links between sinusitis or NPs and asthma will not be considered.

9.1. Epidemiologic evidence

Epidemiologic links between rhinitis and asthma

- The vast majority of asthmatics have rhinitis.
- Many patients with rhinitis have asthma.
- Asthma prevalence is increased in rhinitis, and particularly so in PER and/or moderate/severe rhinitis.
- Allergy is associated with rhinitis and asthma.
- Occupational agents can cause rhinitis and asthma.
- Nonallergic rhinitis is associated with asthma.
- Allergic and nonallergic rhinitis are risk factors for asthma.
- Rhinitis may be associated with nonspecific bronchial hyperreactivity.
- The coexistence of rhinitis with asthma appears to impair asthma control.
- Most asthmatic exacerbations are associated with a nasal viral infection.

9.1.1. Prevalence of asthma in patients with rhinitis. Epidemiologic studies have consistently shown that asthma and rhinitis often coexist in the same patients (1). The prevalence of asthma in subjects without rhinitis is usually $<2\%$. The prevalence of asthma in patients with rhinitis varies from 10% to 40% depending on the study (67, 1882–1884). Patients with a sensitization to indoor and outdoor allergens are more prone to have asthma as a co-morbidity than those with indoor or outdoor allergy (1883). Although all patients with rhinitis may suffer from asthma (1885), patients with moderate/severe PER may be more likely to suffer from asthma than those with IAR and/or a milder form of the disease (67). Mucosal swelling was found to be common in asthmatics (1886).

The difference between rhinitis patients with or without asthma symptoms may be partly related to the perception of dyspnoea in patients with bronchial hyperreactivity (1887).

9.1.2. Prevalence of rhinitis in patients with asthma. The majority of patients with asthma experience rhinitis symptoms (277, 648, 909, 937, 945, 1882, 1888–1899). However, in many instances, symptoms may predominate in one organ and be hidden or unrecognized in other organs even though they exist. In preschool children, nasal symptoms and wheezing may present a different relationship than later in life (1900).

Rhinitis is a factor independent of allergy in the risk for asthma (1, 1901).

However, the results observed in some developing countries may differ from those in western populations (1893, 1902–1904). In these countries, rhinitis and asthma may be independent. However, the prevalence of rhinitis and asthma in rural communities or low-income countries is generally lower than in developed westernized urban communities. A considerable difference between the prevalence of symptoms and the prevalence of medical diagnosis detected in underserved populations may suggest a significant proportion of underdiagnosis, which might be related to a lack of awareness and limited access to health care (903, 1905). In other developing countries like Vietnam (1906), Nigeria (921), Bangladesh (1907) or Brazil (1908), childhood atopy symptom prevalence and links between rhinitis and asthma are similar to those in developed countries.

9.1.3. Rhinitis as a risk factor for the control of asthma. Adults and children with asthma and documented concomitant allergic rhinitis experience more asthma-related hospitalizations and GP visits and incur higher asthma drug costs than adults with asthma alone (1909–1914). These patients also experience more frequent absence from work and decreased productivity. However, some studies have not shown such an association (1915).

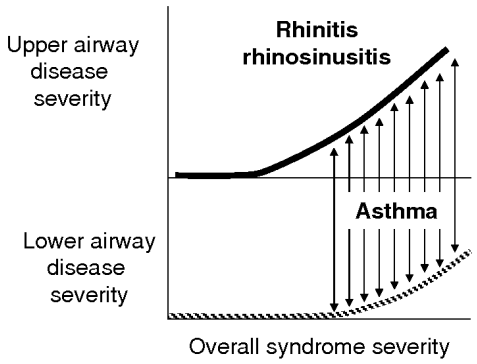

Figure 11. Links between rhinitis and asthma severity.

A model has been proposed to illustrate the relationship between allergic rhinitis and asthma (14; Fig. 11). The basic principle is that the two conditions are manifestations of one syndrome in two parts of the respiratory tract and that the more severe the rhinitis, the more severe the asthma.

9.1.4. Changes in the prevalence of asthma and rhinitis. Several studies have examined the changes in the prevalence of asthma and rhinitis in the same population using identical methods. Results are variable. The ISAAC was repeated for at least 5 years after Phase I to examine the changes in the prevalence of the symptoms of these disorders (853). A rise in the prevalence of symptoms was found in many centers, but an absence of increase in the prevalence of asthma symptoms in the older age group was observed for centers with an existing high prevalence.

Some studies have demonstrated a parallel increasing prevalence of asthma and rhinitis (954, 1916), whereas others have not. Often, it is found that rhinitis prevalence increases faster than asthma prevalence, which was also found to decrease in some countries (904, 947, 948, 1896, 1917–1922). It appears that in regions of highest prevalence, the proportion of subjects suffering from asthma or rhinitis may be reaching a plateau (1919).

The results of four consecutive surveys suggest that the increase in the prevalence of asthma and hay fever in 5- to 7-year-old children living in Switzerland may have ceased. However, symptoms of atopic dermatitis may still be on the rise, especially among girls (957, 1923). Similar findings were observed in Estonia (979).

These studies appear to indicate that the changes in the prevalence of rhinitis and asthma differ but they were not designed to show the variation in the links between the two sites of the airways.

9.1.5. Rhinitis and nonspecific bronchial hyperreactivity. Many patients with allergic rhinitis have an increased bronchial reactivity to methacholine or histamine (939), especially during and slightly after the pollen season (532, 1924–1927). However there are large differences in the magnitude of airway reactivity between asthmatics and rhinitics which cannot be explained by the allergen type or degree of reactivity. Recently, a stronger nasal responsiveness to cold air was observed in patients with rhinitis and asthma, compared to those with rhinitis alone (1928).

Patients with perennial rhinitis have a greater bronchial reactivity than those with seasonal rhinitis (939, 1929). Patients with PER have a greater bronchial hyperreactivity than those with IAR (1930).

Discriminant analysis in allergic rhinitis and asthma can be obtained from the methacholine dose–response (1931).

9.1.6. Allergic rhinitis as a risk factor for asthma. The age of onset of atopy may be an important confounding factor for the development of asthma and rhinitis or rhinitis alone. In infants and very young children, lower respiratory tract symptoms often develop before nasal symptoms (1049). It is difficult to make a clear diagnosis of asthma in this age group. In an Australian study, it was found that atopy acquired at an early age (before the age of 6 years) is an important predictive factor for asthma continuing into late childhood, whereas atopy acquired later was only strongly associated with seasonal allergic rhinitis (250, 1357).

Asthma develops more commonly in patients with rhinitis than in those without. The Children's Respiratory Study (721) showed that the presence of doctor-diagnosed allergic rhinitis in infancy was independently associated with a doubling of the risk of developing asthma by 11 years of age. In children and adults, allergic rhinitis as a risk factor for asthma was shown in a 23-year follow-up of college students (1932). Significantly more (10.5%) of the students originally diagnosed with allergic rhinitis went on to develop asthma compared with 3.6% of those who did not have rhinitis. This study was confirmed by other studies (1358, 1933–1937). In both studies, the onset of asthma was associated with allergic rhinitis, and in the US study, after stratification, rhinitis increased the risk of the development of asthma by about three times among both atopic and nonatopic patients and by more than five times among patients in the highest IgE tertile. Patients with rhinitis, with PER and severe nasal symptoms and with a personal history of doctor-confirmed sinusitis had an additional increased risk of asthma development. The authors concluded that rhinitis is a significant risk factor for adult-onset asthma in both atopic and nonatopic subjects.

It is not clear whether allergic rhinitis represents an earlier clinical manifestation of allergic disease in atopic subjects who will later go on to develop asthma or whether the nasal disease itself is causative for asthma.

The presence of bronchial hyperresponsiveness and concomitant atopic manifestations in childhood increases the risk of developing asthma and should be recognized as a marker of prognostic significance, whereas the absence of these manifestations predicts a very low risk of future asthma (1936, 1938).

9.2. Common risk factors

Asthma and allergic rhinitis share common risk factors. Nonetheless, many studies have provided evidence of some differences in environmental or genetic risks among these related conditions, suggesting a certain degree of specificity of phenotypes. Among the causative agents inducing asthma and rhinitis, some [e.g. allergens and aspirin (1939)] are well known to affect both the nose and the bronchi.

9.2.1. Allergens. Most inhaled allergens are associated with nasal (33) and bronchial symptoms but in epidemiologic studies, differences have been observed.

The role of pollen exposure in asthma is not clear-cut in epidemiologic studies. In contradistinction to allergy to other inhalants, pollen allergy is not usually associated with asthma (285) and chest symptoms were not found to be more common in seasonal rhinitis than in nonrhinitis patients (939). There is an abundant amount of literature confirming that pollen asthma exists (290). Pollen-allergic patients commonly have rhinitis and conjunctivitis during the pollen season. They can also have pharyngitis, cough and wheezing (1940). In most patients, chest symptoms are not associated with a measurable airflow obstruction (1940–1942). Moreover, true asthma exacerbations may occur during dry days in some patients naturally exposed to pollens (1943, 1944), probably because pollen allergens can be born by submicronic particles which can penetrate deeply into the airways (399). Thunderstorm-induced asthma is often, but not always, associated with pollen sensitization (401, 404, 1945–1947).

9.2.2. Occupational agents. Occupational diseases represent an interesting model in the study of the relationship between rhinitis and asthma. Occupational airway diseases include asthma (559), rhinitis (133), COPD (1948) and chronic cough (563). There are many overlaps between the four diseases and it may be difficult to make a clear distinction between them. Moreover, many patients who suffer from occupational and non-OADs are exposed to numerous risk factors and it may not be easy to demonstrate the occupational origin of the disease.

Work-related airway diseases refer to at least two nosologic entities (558):

- occupational asthma and/or rhinitis 'caused' by the workplace (559) and
- asthma (and/or rhinitis) which worsens at work because of other causes (work-aggravated or exacerbated asthma; 560, 561).
- Moreover, work disability is common among adults with severe asthma (559, 560) and rhinitis productivity (84, 562).

Work-related chronic cough is often associated with rhinitis, asthma or COPD, but, as the only symptom, it represents a prevalent work-related airway disease (563, 564).

All of the most common triggers of occupational asthma can induce occupational rhinitis (133). Subjects with occupational asthma may often report symptoms of rhinoconjunctivitis. Rhinitis is less pronounced than asthma with low-molecular-weight agents. On the other hand, rhinitis more often appears before asthma in the case of high-molecular-weight agents such as small mammals (1, 1949). In addition, rhinitis caused by occupational agents will often develop into occupational asthma, highlighting the importance of the cessation of allergen exposure in occupational allergic rhinitis to prevent any intractable asthma.

9.3. Commonalities and differences in the mechanisms of asthma and rhinitis

The nasal and bronchial mucosa present similarities, and rhinitis and asthma are commonly associated. However, the nose and bronchi have a different embryologic origin (1950), smooth muscle is present only in the bronchi and there are differences between rhinitis and asthma.

Commonalities and differences in mechanisms between rhinitis and asthma

- Most asthmatics have rhinosinusitis as demonstrated by CT scans.
- Severe asthmatics have more severe rhinosinusitis than mild asthmatics.
- Eosinophilic inflammation is present in the nasal and bronchial mucosa of asthmatics.
- Epithelium and basement membrane differ in the nasal and bronchial mucosa of asthmatics.
- The bronchial and nasal mucosa of COPD patients appear to be similar.
- Endobronchial challenge in rhinitis patients induces a bronchial reaction.
- Bronchial challenge induces nasal inflammation.
- Nasal challenge induces bronchial inflammation.
- Allergic inflammation has a systemic component.

9.3.1. Common pathways

9.3.1.1. IgE-mediated allergy. Allergic asthma and rhinitis are commonly associated with raised circulating levels of IgE, and the increased presence of total serum IgE is a risk factor for asthma even in nonallergic individuals (1951, 1952). Allergen-specific IgE is a prerequisite for the development of allergic inflammation in both allergic rhinitis and asthma (see Chapter 4.1.1).

9.3.1.2. Cysteinyl leukotrienes. Cysteinyl leukotrienes are a family of inflammatory lipid mediators (LTC_4, LTD_4 and LTE_4) synthesized from arachidonic acid by a variety

of cells, including mast cells, eosinophils, basophils and macrophages. Cysteinyl leukotrienes are multifunctional mediators in allergic rhinitis (803) and asthma (1953, 1954). They are released from inflammatory cells that participate in allergic rhinitis and asthma (1955). Receptors for CysLT are located in nasal and bronchial tissues. They are increased in patients with allergic rhinitis and asthma and are released following allergen exposure. The administration of CysLT reproduces the symptoms of allergic rhinitis and asthma. Cysteinyl leukotrienes predominate in both the early and late phases of the allergic response. These mediators play a role in the maturation and tissue recruitment of inflammatory cells, as well as in the complex inter-regulation between CysLT and a variety of other inflammatory mediators.

9.3.1.3. Nitric oxide. Nitric oxide was initially described as an endothelium-derived relaxing factor (1956). It is now demonstrated that NO has a potent regulatory role in a wide variety of functions and tissues (1957) and is produced during inflammation (1958, 1959). It is produced in the nose (1960, 1961) and paranasal sinuses (1962). Nitric oxide levels are increased during allergic rhinitis and other pathologic conditions of the nose including rhinosinusitis (123, 1963).

High levels of NO can be found in exhaled air and most are derived from the paranasal sinuses (1964) suggesting that there may be interactions between the upper and lower airways (14). Nitric oxide produced in the upper airways may play a protective role for the entire respiratory tract. It has strong bacteriostatic and antiviral activities (1965, 1966), in particular on rhinoviruses (1967, 1968). It improves oxygenation (1969), exerts bronchodilatory activities (1970) and modulates lower airways responsiveness.

9.3.2. Similarities and differences of nasal and bronchial inflammation in asthma and rhinitis. In normal subjects, the structure of the airways mucosa presents similarities between the nose and the bronchi. Both nasal and bronchial mucosa are characterized by a pseudo-stratified epithelium with columnar, ciliated cells resting on a basement membrane. Underneath the epithelium, in the submucosa, vessels and mucus glands are present with structural cells (fibroblasts), some inflammatory cells (essentially monocytic cells, lymphocytes and mast cells) and nerves (14, 1971, 1972).

There are also differences. In the nose, there is a large supply of subepithelial capillaries, arterial systems and venous cavernous sinusoids. On the other hand, smooth muscle is present from the trachea to the bronchioles (1973).

In asthma and rhinitis, inflammation of the nasal and bronchial mucosa is sustained by a similar inflammatory infiltrate including eosinophils, mast cells, T lymphocytes, cells of the monocytic lineage (1972, 1974), similar proinflammatory mediators (histamine, CysLT), Th2 cytokines and chemokines (767, 1972, 1975–1977).

However, the magnitude of inflammation may not be identical. In patients with moderate–severe asthma, eosinophilic inflammation is more pronounced in the bronchi than in the nose (815), whereas in patients with mild asthma, inflammation appears to be similar in both sites. Moreover, eosinophilic inflammation of the nose exists in asthmatics with or without nasal symptoms (1978).

To determine whether nasal inflammation in asthma was related to asthma only or was found commonly in other bronchial diseases, nasal inflammation and sinus involvement were studied in patients with COPD. Less than 10% of the patients with COPD had nasal symptoms. In patients with COPD, the nasal and bronchial mucosa presented similar features with epithelial metaplasia and increased inflammatory cells ($CD8^+$ T-cells and neutrophils; 1979). Computerized tomography scans showed few abnormalities in COPD. Thus, nasal and sinus inflammation seen in asthmatics is related to asthma and is not a feature of all bronchial diseases (Table 29).

Table 29. Nasal and bronchial mucosa in asthma

		Nasal mucosa (rhinitis/asthma)	Bronchial mucosa (asthma)
Epithelium	Shedding	Variable, often minimal	Common, in particular in severe disease
	Metaplasia	Sometimes	Very rarely
Basement membrane	Collagen IV	Normal	Normal
	Collagen III, V, fibrous proteins	Pseudo-thickening may occur, but limited	Pseudo-thickening very common
Submucosa	Eosinophils	Often present	Often present
	CD4+ T-cells	Commonly increased	Commonly increased
	CD8+ T-cells	Low numbers	Low numbers
	Elastase + cells	Sometimes increased numbers	Usually low numbers
	CD68+ cells	Sometimes increased numbers	Often increased numbers
	Collagen deposition	Possible	Common but not extensive
	Fibroblasts	Possibly increased numbers	Increased numbers
	Myofibroblasts	?	Present
	Smooth muscle	None (except around blood vessels)	Metaplasia and hyperplasia

9.3.3. Bronchial inflammation in rhinitis. Some studies have examined the bronchial mucosa in atopic nonasthmatic patients or in patients with allergic rhinitis. They have all combined to indicate that there was a slight increase in the basement membrane size and a moderate eosinophilic inflammation (1980–1984). Natural exposure to pollen during season provokes an increase in airway responsiveness in nonasthmatic subjects with seasonal allergic rhinitis and also induces inflammatory cell recruitment and IL-5 expression, leading to bronchial inflammation (1985). An eosinophilic inflammation, remodeling of the lower airways, bronchial responsiveness and cough reflex sensitivity were all observed in nonasthmatic subjects with nasal allergy (1986).

9.3.4. Nasal and bronchial remodeling. Remodeling is defined as 'model again or differently, reconstruct' (1987). This is a critical aspect of wound healing, representing a dynamic process which associates ECM production and degradation. Remodeling usually occurs in reaction to an inflammatory condition which in turn leads to a normal reconstruction process (model again) or a pathologic process (model differently) and is not necessarily associated with fibrosis. Remodeling therefore exists in all inflammatory diseases but its control differs largely depending on the disease.

In 1992, it was proposed that asthma, a chronic inflammatory disease, was associated with abnormal airways remodeling (1987) and it took several years to understand the concept of 'remodeling'. Bronchial remodeling always exists in asthma, whereas it may not be clinically demonstrated (1972, 1976). However, nonspecific bronchial hyperreactivity, a feature associated with airway remodeling, is almost always present in asthma (1988). In allergic rhinitis, remodeling is still poorly understood (19, 808, 809). Even though inflammation is similar in allergic rhinitis and asthma, nasal remodeling as well as its clinical consequences are less extensive in the nose by comparison to those of the bronchi (see Chapter 4.1.7).

9.3.5. Allergy as a local disease. Endobronchial allergen challenge carried out on nonasthmatic patients with seasonal rhinitis induced bronchoconstriction (1989) and the secretion of proinflammatory mediators and cytokines as well as the recruitment of inflammatory cells in the lavage fluid (1990–1992). These studies combine to indicate that patients with nasal symptoms can develop asthma only if the allergen is properly administered into the airways. It may be argued that the doses of allergen inducing these bronchial reactions are far greater than those naturally occurring during allergen exposure. This situation seems to exist in thunderstorm-induced asthma (401) which has been associated with grass pollen allergy (404). The aerodynamic size of pollen grains ranges from 10 to 100 μm and only a fraction of them can be deposited into the bronchi, thus most patients have only rhinitis with no asthma. However, when exposed to water, pollen allergens are released in submicronic particles, starch granules, which can reach the lower airways and induce asthma (400).

It is presently unknown as to which factors determine the occurrence and persistence of asthma in HDM-allergic individuals. The difference in bronchial inflammation between asthma and nonasthmatic rhinitis appeared to be more closely related to indices for neutrophilic inflammation (1993).

9.3.6. Allergy as a systemic disease: bidirectional relationship between nasal and bronchial inflammation. Endobronchial allergen challenge can induce nasal and bronchial symptoms as well as reductions in pulmonary and nasal function (1994, 1995). In this study, the number of eosinophils increased in the challenged bronchial mucosa, in the blood and in the nasal mucosa 24 h after bronchial challenge. Moreover, eotaxin-positive cells in the nasal *lamina propria* and an enhanced expression of IL-5 in the nasal epithelium were found 24 h after bronchial challenge.

Nasal allergen challenge can induce bronchial inflammation (1996–1998).

In patients with allergic diseases, allergen provocation can activate a systemic response that provokes inflammatory cell production by the bone marrow (1994, 1995, 1998–2000). After the release and differentiation of progenitor cells, eosinophils, basophils and mast cells are typically recruited to tissues in atopic individuals. An understanding at the molecular level of the signaling process that leads to these systemic responses between the target organ, especially the airways, and the bone marrow may open up new avenues of therapy for allergic inflammatory disease (2001). Studies that support the critical involvement of the bone marrow in the development of eosinophilic inflammation of the airways point out the systemic nature of these conditions.

Patients with asthma have an inflammation of the salivary glands (2002) and the gut (2003) suggesting a generalized inflammation of the mucosal system.

A second important mechanism may be involved in the systemic origin of airway inflammation. *In situ* haemo-

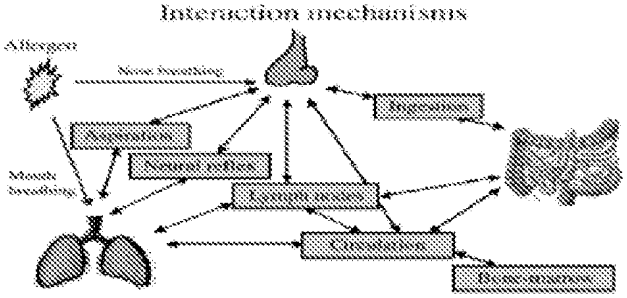

Figure 12. Systemic interactions of allergic diseases [from Braunstahl et al. (2007)].

poiesis (2004) depends on the production of haemopoietic cytokines by inflamed tissues from patients with allergic rhinitis (2005) which, by generating a particular local 'microenvironment', promote the differentiation and maturation of eosinophil progenitors that populate the nasal or the bronchial mucosa (2006).

It is therefore likely that a truly 'systemic' response to the application of inflammatory stimuli to the nasal (or bronchial) mucosa should be associated with an activation of the aforementioned mechanisms (Fig.12).

9.4. Impact of nasal function and dysfunction on the lower airways

The most important concepts regarding nose–lung integration are the anatomical similarities and the functional complementarity that assigns the role of the protector of the lung to the nose. This role is achieved through a variety of functional characteristics of the nose (2008) which include warming and humidification, filtering and mucociliary clearance as well as air conditioning of the lower airways. Besides inflammatory processes, protective functions of the nose may impair the lower airways and explain some of the links between rhinitis and asthma.

Impaired nasal mucosal air conditioning has only been shown indirectly (2009) and its role on the lower airways is not yet clear. Patients with chronic nasal disease suffer from decreased mucociliary clearance (2010) but no study exists showing its effect on the lower airways. The nasal passages of asthmatics have a decreased ability to warm and humidify inspired air (2011).

Impaired air warming and humidification by the nose may have some important effects (2012). A stronger nasal responsiveness to cold air was found in patients with rhinitis and asthma, when compared to those with rhinitis alone (1928). In patients with asthma, but not in healthy subjects, provocation with cold air in the nose causes bronchoconstriction while warm air causes bronchodilation (2013). These findings have suggested the existence of a nasobronchial reflex (2014) which has not been demonstrated (2015). Increasing the transfer of heat and water in the lower respiratory tract alters the bronchial and nasal function in a linked fashion. Forcing the nose to augment its heat-exchanging activity does reduce nasal caliber but has no effect on the intrathoracic airways (2016). Nasal breathing protects against exercise-induced bronchospasm (2017, 2018).

The filtering of particles and gaseous materials in inhaled air is another major function of the air-conditioning capacity of the nose. The beneficial effect of nose breathing by comparison to mouth breathing has been shown in exercise-induced asthma (2017–2019) and to a lesser extent in SO_2-induced asthma (2020, 2021).

It therefore appears that the alteration of nasal function has only a small effect on the lower airways.

9.5. Clinical consequences

Effect of rhinitis and asthma on quality of life

- QOL is impaired in asthma.
- QOL is impaired in rhinitis.
- The physical component of QOL is impaired in asthma.
- The social component of QOL is impaired in rhinitis.

Quality of life has been found to be impaired in patients with asthma and in patients with allergic rhinitis, and the relative burden of these diseases has recently been studied using the generic SF-36 questionnaire in the ECRHS, a population-based study of young adults (87). Patients with both asthma and allergic rhinitis experienced more physical limitations than patients with allergic rhinitis alone, but no difference was found between these two groups regarding concepts related to social/mental health. Subjects with asthma but without rhinitis could not be studied as their number was too low. However, it seems that impairment in the social life of asthmatics may be attributable to nasal symptoms.

Significant deterioration in rhinoconjunctivitis-specific QOL was observed through the pollination period in patients with allergic rhinitis and asthma. At pollen peak, patients with asthma experienced significantly worse physical functioning than patients with rhinitis alone (2022).

9.6. Therapeutic consequences

Treatment of rhinitis and asthma using a single approach

- Oral H_1-antihistamines are not recommended, but not contraindicated in the treatment of asthma.
- Intranasal glucocorticosteroids are at best moderately effective in asthma.
- Intranasal glucocorticosteroids may be effective in reducing asthma exacerbations and hospitalizations.
- The role of intrabronchial glucocorticosteroids in rhinitis is unknown.
- Montelukast is effective in the treatment of allergic rhinitis and asthma in patients over 6 years of age.
- Subcutaneous immunotherapy is recommended in both rhinitis and asthma in adults, but it is burdened by side effects, in particular in asthmatics.
- Anti-IgE monoclonal antibody is effective for both rhinitis and asthma.

Although asthma and allergic rhinitis commonly occur together, treatments for one of the conditions could potentially alleviate the coexisting condition.

Medications for asthma and rhinitis can be administered via local (intranasal, intraocular) or inhaled (intrabronchial), oral and parenteral routes. There are advantages (and certain drawbacks) when the drug is administered directly into the target organ (1). Moreover, some drugs like cromoglycate or nedocromil are not absorbed when given orally and are effective only when administered locally. In patients suffering from asthma and rhinitis, the local administration of drugs requires that they should be administered both nasally and bronchially and this may decrease compliance to treatment which is already low in asthma and rhinitis.

9.6.1. Drugs administered topically. Glucocorticosteroids are the most effective drugs for the treatment of rhinitis and asthma when administered topically in the nose and the bronchi. The intranasal treatment of rhinitis using glucocorticosteroids was found to improve asthma at best moderately in some but not all studies (2023, 2024). Symptoms and pulmonary function tests were inconstantly improved. However, a number of aspects, such as the extent to which the pathophysiology of the two diseases overlaps and whether treating one will affect the other, still remain to be clarified (2025).

Less is known about the effects on nasal disease of inhaled (intrabronchial) treatment with glucocorticosteroids. A study examined the effects on nasal allergic disease of inhaled budesonide (avoiding nasal deposition of the drug) in patients with seasonal allergic rhinitis, but without asthma (2026). During the birch pollen season, budesonide reduced the seasonal eosinophilia both in the circulation and in the nose along with an attenuation of seasonal nasal symptoms. However, this study was not confirmed (2024).

9.6.2. Drugs administered orally. Drugs administered by the oral route may have an effect on both nasal and bronchial symptoms (2027). Oral H_1-antihistamines represent the first-line treatment of allergic rhinitis but although studies have found some effect on asthma symptoms (1942, 2028–2030), many negative studies are unpublished and pulmonary function tests are unchanged. These drugs are not recommended for the treatment of asthma (2031, 2032). The association of oral H_1-antihistamines and decongestants was found to be effective on asthma symptoms (2033).

Several pivotal studies were carried out to assess the efficacy of leukotriene receptor antagonists in seasonal and perennial allergic rhinitis (see Chapter 7.2.5). In studies carried out on patients with seasonal allergic rhinitis and asthma, montelukast was found to improve nasal and bronchial symptoms (1588, 1589). As-needed ß-agonist use (puffs/day) was also reduced with montelukast. In the COMPACT trial, in a subgroup of asthmatic patients with allergic rhinitis, a combined treatment approach that included montelukast and budesonide provided significantly greater efficacy in reducing airflow obstruction when compared to doubling the dose of budesonide (2034). A *post hoc* analysis of a 52-week, double-blind multicenter clinical trial (IMPACT) showed that the presence of self-reported concomitant rhinitis in patients with asthma resulted in a higher rate of asthma attacks and more emergency room visits compared to asthma patients without concomitant rhinitis (1909).

Oral glucocorticosteroids are highly effective in the treatment of rhinitis and asthma but side effects are common after long-term use.

9.6.3. Specific immunotherapy. The indications of specific immunotherapy in allergic asthma and rhinitis have been separated in some guidelines (9, 2035). This artificial separation has led to unresolved issues (2036–2039) possibly because the allergen-induced IgE-mediated reaction has not been considered as a multiorgan disease. It is therefore important to consider specific immunotherapy based on the allergen sensitization rather than on the disease itself because most patients with allergic asthma also have rhinitis or rhinoconjunctivitis (1649). Several controlled studies have investigated the efficacy of allergen vaccination in asthma, and rhinitis improved in the same patients (1102, 1655, 2040–2046).

The indications for immunotherapy in asthma are hampered by safety issues (1678). Most guidelines propose not to use immunotherapy in patients with severe or uncontrolled asthma because of the risk of severe bronchial reactions using subcutaneous immunotherapy (2047–2049). One study was safe and effective in patients with moderate-to-severe asthma (2050). Sublingual immunotherapy may be safe in patients with moderate-to-severe asthma, but more data are needed. Moreover, pharmacotherapy is highly effective and safe in patients with mild or moderate asthma. Thus, there is little place for immunotherapy in asthma alone although a study has shown that a standardized mite extract could be effective and safe in patients with moderate-to-severe asthma. On the other hand, most patients with asthma have rhinitis and the indication for moderate/severe rhinitis and mild asthma is indicated.

When allergen vaccination is introduced to patients who only have allergic rhinoconjunctivitis, the development of asthma may be prevented. The early study of Johnstone and Dutton (2051) using several different allergens showed that after 3 years of treatment, children receiving pollen allergen vaccination developed less asthma than the control group. The PAT study showed that 3 years of immunotherapy with standardized allergen extracts of grass and/or birch shows a long-term clinical effect and preventive effect on the development of asthma in children with pollen rhinoconjunctivitis (1688, 1689). Another study using sublingual vaccination with HDMs

also showed the prevention of asthma (1730). More data are needed to make a recommendation with SLIT.

9.6.4. Anti-IgE monoclonal antibody. The anti-IgE antibody, omalizumab (768, 770), has been shown to be effective in patients with allergic rhinitis and moderate/severe allergic asthma. Its systemic activity and ability to reduce levels of IgE regardless of allergen specificity may be interesting in these respects.

9.6.5. The treatment of rhinitis reduces asthma severity. Three *post hoc* analysis studies have shown that treating allergic rhinitis reduces healthcare utilization for co-morbid asthma (2052–2054). In a first study, a retrospective cohort study was carried out on 4 944 patients with both allergic rhinitis and asthma, aged 12–60 years, who were continuously enrolled and had no evidence of COPD (2052). The risk of an asthma-related event (hospitalization and emergency department visit) for the treated group was about half that for the untreated group. In another retrospective cohort study carried out on 13 844 asthmatics of a managed care organization aged > 5 years (2053), patients who received intranasal glucocorticosteroids had a reduced risk for emergency department visits by comparison to those who did not receive this treatment. However, a bias may exist in observational studies on the effectiveness of nasal glucocorticosteroids in asthma (2055).

9.7. Costs

Rhinitis was found to increase the costs of asthma (1131, 2056) but more data are needed.

9.8. Rhinitis and asthma: a continuum of disease?

There are similarities and differences between the nasal and bronchial mucosa in rhinitis and asthma. It appears that most asthmatics experience rhinitis, whereas only a fraction of rhinitis patients have clinically demonstrable asthma even though a greater number of patients have nonspecific bronchial hyperreactivity. It seems that the epithelial–mesenchymal trophic unit exists from the nose to the bronchiolar–alveolar junction and that the same inflammatory cells are present throughout the airways suggesting a continuum of disease. Some mediators such as NO can exert action in the entire airways.

However, there are differences in terms of exposure of allergens and noxious agents, the nose being more exposed than the lower airways. There are also major structural differences between the nasal and the bronchial mucosa because in the former there is a large vascular supply, whereas in the latter there is smooth muscle. Airway smooth muscle is of paramount importance in asthma because of its contractile properties, but in addition, it may contribute to the pathogenesis of the disease by increased proliferation and by the expression and secretion of proinflammatory mediators and cytokines.

The embryologic origin of the nose and the lower airways differs and may explain some differences in remodeling between these two sites.

These studies strongly support the 1999 WHO workshop 'Allergic Rhinitis and its Impact on Asthma' (1) which recommended:

- 'that patients with PER should be evaluated for asthma by history, chest examination and, if possible and when necessary, assessment of airflow obstruction before and after bronchodilator;
- that history and examination of the upper respiratory tract for allergic rhinitis should be performed in patients with asthma and
- to propose a strategy combining the treatment of both the upper and the lower airway disease in terms of efficacy and safety'.

The perception of patients and doctors on the links between asthma and rhinitis varies between countries, but acceptance appears to be higher than expected (2057, 2058). However, knowledge is not directly translated into practice because fewer doctors co-prescribe treatments for rhinitis and asthma in the same patient.

9.9. Management of asthma and rhinitis in athletes

Elite athletes commonly use drugs to treat asthma, exercise-induced bronchial symptoms and rhinitis. Only a few controlled studies have been conducted on the effects of antiasthma drugs on asthma symptoms, bronchial hyperresponsiveness and airway inflammation in elite athletes. Inhaled $ß_2$-agonists and leukotriene receptor antagonists are effective against exercise-induced bronchoconstriction (2059). In contrast, airway inflammation, bronchial hyperresponsiveness and symptoms have responded poorly to inhaled glucocorticosteroids (2060) and leukotriene antagonists (2061). A single dose of montelukast attenuated bronchoconstriction from either exercise or Eucapnic Voluntary Hyperventilation (2062). As discontinuing high-level exercise has proved effective in reducing eosinophilic airway inflammation, exercise or training should be restricted in athletes having troublesome symptoms and sputum eosinophilia.

Since 2001, the International Olympic Committee-Medical Commission (IOC-MC) has required athletes using inhaled $ß_2$-agonists to provide clinical evidence of their asthmatic condition (2063). The distinction between oral (prohibited in sport) and inhaled salbutamol is possible, but athletes must be warned that an excessive use of inhaled salbutamol can lead to urinary concentrations similar to those observed after oral administration. About 10 653 athletes competed in Athens; 4.2% were approved the use of a $ß_2$-agonist and 0.4% were rejected. This approval rate was 26% less than the notifications in 2000 in Sydney (5.7%; 2064). There is ample use of doctor-prescribed medications in Finnish elite athletes (2065) but there are no signs of inhaled $ß_2$-agonist overuse (181).

The purpose of the World Anti-Doping Code 2003 and the 2004 Prohibited List was to create a universal international standard to fight doping in competitive sports. This has resulted in a series of changes for doctors regarding their work with competitive athletes. The revised definition of doping now includes doctors in the group of persons who can fulfil the elements of a doping offence (2066). The list of permitted and prohibited antiallergic treatments is given in Table 28.

Switching the location of training to one with less irritating environmental factors should be considered whenever possible. It appears to be difficult to change the 'natural course' of asthma in athletes by anti-inflammatory treatment (2059).

9.10. Diagnosis of asthma in rhinitis patients

Unfortunately, the underdiagnosis of asthma is common around the world (2067–2070) and many patients might have been diagnosed with asthma if the links between the upper and lower airways had been recognized.

Due to the reversibility of airflow obstruction, the diagnosis of asthma is difficult and great attention should be focused on the history of paroxysmal attacks of breathlessness commonly associated with chest tightness and wheezing, particularly at night and in the early hours of the morning. However, these common symptoms are not pathognomonic by themselves. A history of recurrent exacerbations (or attacks) may be provoked by nonspecific triggers such as allergens, irritants, exercise and virus infections. On the other hand, asthma symptoms are reversible spontaneously or under treatment.

In all patients with PER, asthma should be routinely investigated by history and, if needed, using pulmonary function tests assessing the reversibility of airflow obstruction under inhaled short-acting β_2-agonists. Patients with IAR have an increased risk of developing asthma when compared to subjects without rhinitis. Questions regarding asthma should also be asked.

A simple questionnaire may be used for screening (Fig. 13). However, more structured questionnaires have been validated (2071).

Physical findings that suggest the diagnosis of asthma include clinical signs of dyspnoea, airflow limitation (wheezing) and hyperinflation. However, some patients may have a normal chest auscultation and, conversely, wheezing may be absent in very severe asthma exacerbations.

However, the diagnosis of asthma is confirmed by the demonstration of a reversible airflow obstruction which can easily be performed in patients of over 5 years of age (1428) using the following tests: FEV_1, its accompanying forced vital capacity (1428, 2072, 2073) and the peak expiratory flow (1428, 2074). These tests can be used for recording the reversibility of airway obstruction after inhaled short-acting β_2-agonists. The diurnal variation of lung function using peak flow is another option.

Although FEV_1 is the most robust test in the assessment of airflow obstruction, it may not be sensitive enough to detect it in some patients with allergic rhinitis who may just have an obstruction of the small airways (2075, 2076).

The diagnosis of asthma in patients with rhinitis is usually determined by the GP but also by specialists including ENT doctors. Whether the diagnosis of asthma requires confirmation by a specialist depends on the level of control of the asthma as well as the healthcare system. It varies from country to country.

Although it is optimal to perform a pulmonary function test with reversibility in all asthmatics, one of the major issues is the place of spirometry in the evaluation of asthma in patients with rhinitis, as most

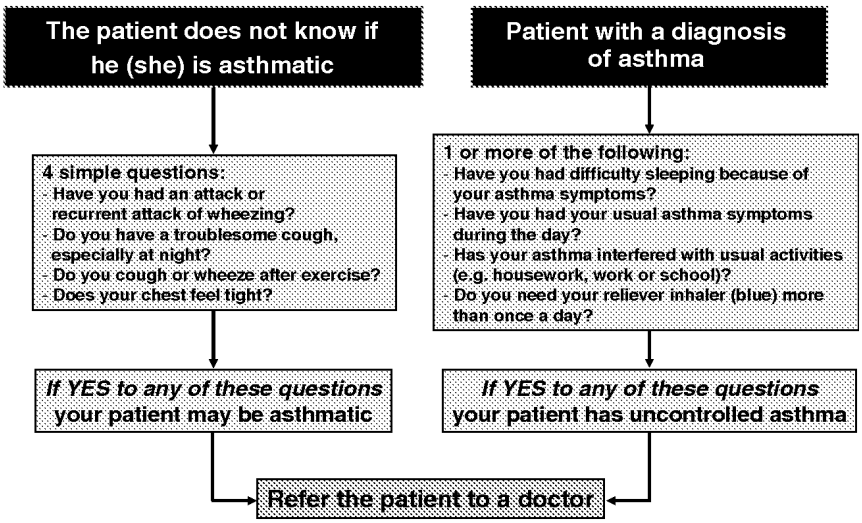

Figure 13. Diagnosis of asthma in patients with rhinitis.

general practitioners and ENT doctors do not have the necessary equipment to measure pulmonary function. It is possible to use structured questionnaires (2077) to make a relatively precise diagnosis of asthma in adolescents and adults. However, if a patient has a past history of severe asthma and/or signs of uncontrolled asthma, pulmonary function tests are needed.

Patients with rhinitis develop asthma more often than those without the disease, and a regular follow-up of patients with PER should include asthma assessment. Doctors should inform patients with rhinitis of the signs of asthma symptoms which may occur.

10. Other co-morbidities and complications

- Allergic conjunctivitis is a common co-morbidity of allergic rhinitis.
- The other forms of conjunctivitis are not associated with an IgE-mediated allergic reaction.
- Although the sinus may be involved during an allergic reaction, the role of allergy as a risk factor for CRS is still unknown.
- Allergy does not appear to be a risk factor for NP.
- The role of allergy as a risk factor of otitis media with effusion (OME) is unknown.
- Chronic cough can be caused by several etiologies including allergic rhinitis and CRS.

Co-morbidities can be classified as common causal pathways (e.g. allergy) or as complicating co-morbidities (complication of infection due to mucosa swelling, stasis of mucus; 2078).

10.1. Conjunctivitis

Ocular symptoms usually referred to as 'conjunctivitis' can be caused by allergic and nonallergic agents. Moreover, allergic eye diseases represent a heterogeneous entity including different forms of conjunctivitis with different mechanisms, symptoms and signs, pathophysiology, degree of severity and response to treatment (2079–2082). Conjunctivitis is usually classified as acute, allergic, vernal or atopic. An immunologic mechanism has also been postulated for conjunctival symptoms in contact lens wearers (Table 30).

Acute allergic conjunctivitis is an acute hypersensitivity reaction with hyperemia and chemosis accompanied by an intense tearing, itching and burning of the eye, caused by an accidental exposure to several substances such as gas and liquid 'irritants' or animal danders.

Allergic conjunctivitis is the typical conjunctival reaction in allergic rhinitis, rhinoconjunctivitis or following exposure to allergens. Ocular symptoms occur in a large proportion of patients with rhinitis. Allergic conjunctivitis is more common with outdoor allergens than with indoor allergens. In some studies on pollen allergy, conjunctivitis is sometimes present in over 75% of patients suffering from rhinitis. However, the prevalence of the association between rhinitis and conjunctivitis cannot be easily defined, because conjunctival symptoms are often considered to be of minor importance (2083), and are possibly not spontaneously reported by patients with rhinitis and/or asthma in medical interviews or in questionnaire-based epidemiologic studies such as the ISAAC and the ECRHS (45, 914). Accordingly, the association between rhinitis and conjunctivitis is largely underestimated in epidemiologic studies.

Vernal keratoconjunctivitis is a severe bilateral eye condition in children with frequent involvement of the cornea (vernal keratoconjunctivitis) characterized by conjunctival hypertrophy and mucus excess (2084). It is found in all countries of the world (2085, 2086). It is often associated with other allergic diseases but the relationship between atopy and vernal keratoconjunctivitis is not demonstrated. Cysteinyl leukotrienes may play a role in this disease since an open study found that montelukast improved vernal keratoconjunctivitis (2087).

Atopic conjunctivitis is a keratoconjunctivitis associated with eczematous lesions of the lids and skin (2088).

Contact lens conjunctivitis is a giant-papillary conjunctivitis observed in hard and soft contact lens wearers. The prevalence of rhinitis in patients with atopic and

Table 30. Pathophysiology and nosography of allergic conjunctivitis

	Pathophysiology	Tarsal conjunctiva	Cornea	Eyelids
Allergic conjunctivitis	IgE, mast cells, eosinophils	+	–	+
Vernal keratoconjunctivitis	Th2, eosinophils; IgE	++	++	+
Atopic keratoconjunctivitis	IgE, mast cells, basophils, Th2 + Th1 Microbial antigens?	++	+++	++
Giant papillary conjunctivitis	T lymphocytes (Th0?), leukotrienes; mechanical inflammation?	++	±	–
Contact blepharoconjunctivitis	Dendritic cells, Th1	±	±	+

contact lens conjunctivitis is similar in allergic and nonallergic patients (2083).

10.2. Rhinosinusitis

The role of allergy in sinus disease is still unclear (15, 31, 2089). It has been speculated that nasal inflammation induced by IgE-mediated mechanisms favors the development of acute and/or chronic sinus disease. A similar inflammation is observed in the nose and sinuses of patients with allergic rhinitis (2090–2095). Moreover, sinus involvement has been observed by CT scans in allergic patients during the ragweed pollen season (2096). Nasal challenge with allergen induces a sinus reaction demonstrated by CT scans (2097). Total IgE serum levels correlate with the sinus mucosal thickness on CT scans (2098). However, at present, it remains incompletely understood whether and via which mechanisms the presence of allergic inflammation in the nose predisposes the individual to the development of sinus disease.

Epidemiologic studies concerning CRS are inconclusive and, so far, there are no published prospective reports on the incidence of infectious rhinosinusitis in populations with and without clearly-defined allergy. Several epidemiologic studies report a high prevalence of sensitization to inhalant allergens both in acute (2099) and CRS patients (2100, 2101). Prevalence for sensitization to inhalant allergens is reported in up to 84% of patients undergoing revision sinus surgery (2102). Compared to the general population where CRS is estimated to be found in up to 6% of subjects (2103–2106), patients sensitized to inhalant allergens seem to experience more sinus complaints. On the basis of these epidemiologic observations, one may not however conclude that allergic rhinitis predisposes to the development of CRS as these studies include a large referral bias. A predominance of allergy to perennial *vs* seasonal allergens was found in chronic sinusitis patients at the time of indication for surgery (2102). Moreover, epidemiologic studies failed to demonstrate a higher incidence of sinus disease during the pollen season in pollen-sensitized patients (2100).

The role of molds in CRS is unclear. Fungal elements are one of the causative agents of CRS, possibly by an allergic mechanism (2107–2110), but controversy has accumulated concerning the prevalence of fungal CRS (2111, 2112) and benefits of topical amphotericin B therapy are inconsistent (2113, 2114).

Only a limited number of studies examined the effect of antiallergic therapy in atopic patients with sinus disease. Loratadine, as an adjunctive therapy of atopic patients with acute sinusitis, was found to modestly improve sneezing and nasal obstruction (2115). It is also noteworthy to mention that half of the allergic patients with a history of sinus surgery and undergoing immunotherapy believed that surgery alone was not sufficient to completely resolve the recurrent episodes of infection related to their sinus disease (2116). Well-conducted clinical trials showing beneficial effects of oral H_1-antihistamines in patients with CRS are lacking.

Notwithstanding the lack of precise insight into mechanisms, symptoms of IgE-mediated allergic inflammation should be requested during history taking in patients with CRS, and skin prick tests or specific IgE should be performed in the case of clinical suspicion (evidence D).

In spite of limited evidence regarding the effectiveness of antiallergic therapy in patients with chronic sinus disease, it would seem logical to add an antiallergic therapy to the treatment scheme of patients with chronic sinus disease and concomitant allergy.

10.3. Nasal polyps

Nasal polyps are considered as a chronic inflammatory disease of the sinonasal mucosa, being part of the spectrum of chronic sinus pathology (31). The role of allergy in the generation of NPs is even more unclear than in CRS (15). Historically, NPs were believed to develop as a result of an allergic reaction to an unknown stimulus, giving rise to mucosal swelling and protrusion of the sinonasal mucosa into the nasal cavity. Both allergic rhinitis and NPs are characterized by an inflammatory response that shows many similarities (2117). However, until now, no clear epidemiologic data support a role of allergy in NPs.

10.4. Adenoid hypertrophy

The adenoid, the peripheral lymphoid organ located in the nasopharynx, is part of the Waldeyers ring and contributes to the development of immunity against inhaled micro-organisms in early life (2118). Many triggers, including microbial stimuli such as molds (2119) or external irritants like cigarette smoke (2120), have been related to the enlargement of adenoid tissue and hence to the development of symptoms. Symptoms related to adenoid hypertrophy range from nasal obstruction, *rhinolalia clausa*, open-mouth breathing and snoring to the so-called 'adenoid facies'. In children, both allergic rhinitis and adenoid hypertrophy may give similar symptoms and therefore need to be differentiated at the time of the consultation.

Little is known about the correlation between allergic rhinitis and adenoid hypertrophy in children. The presence of sensitization to inhalant allergens has been reported to alter the immunology of adenoid tissue. $CD1a^+$ Langerhans cells and eosinophils are increased in the adenoids of allergic children (2121, 2122). Similarly, eosinophils, IL-4 and IL-5 mRNA-positive cells are increased in the adenoids of atopic children (2122). Furthermore, atopy is associated with increased numbers of IgE-positive cells in adenoids, irrespective of the presence of adenoid hypertrophy (2123). However, no

correlation is observed between the atopic state and the degree of adenoid hypertrophy (2124).

Although the role of allergy is unclear in adenoid hypertrophy, allergy should be investigated in children with symptomatic adenoid hypertrophy.

Properly-conducted clinical trials on oral H_1-antihistamines in allergic children with allergic rhinitis and adenoid hypertrophy are lacking. In contrast, intranasal glucocorticosteroids are capable of reducing adenoid-related symptoms (2125–2127) with no differences in response between atopic and nonatopic children (2125). In these studies, the effects of intranasal glucocorticosteroids on symptoms of allergic inflammation in the nose and adenoids cannot be dissociated from their anti-inflammatory effects on the adenoids themselves. Recently, a short treatment with oral steroids, followed by a prolonged oral H_1-antihistamine and intranasal glucocorticosteroid spray therapy, was found to reduce the adenoid volume and associated symptoms (2128).

10.5. Tubal dysfunction

The Eustachian tube exerts a major function in middle-ear homeostasis via its role in the ventilation and protection of the middle-ear and mucociliary clearance. In line with the concept of global airway allergy, the Eustachian tube lined with respiratory epithelium may be involved in the allergic response following allergen inhalation. The mucosal lining in the tubarian tube, i.e. the nasopharyngeal orifice of the Eustachian tube, contains an allergic inflammatory infiltrate in allergic rhinitis patients (2122). It is therefore not surprising that allergic inflammation with concomitant mucosal swelling may impair the function of the Eustachian tube. Allergic rhinitis patients have a higher risk of Eustachian tube dysfunction assessed by tympanometry than nonallergic subjects, particularly during childhood (2129).

Nasal challenge with HDM induces nasal obstruction and tubal dysfunction in allergic individuals (2130). At present, it remains to be elucidated as to whether nasal allergen inhalation leads to the deposition of allergens in the tubarian tube with induction of a local allergic response, or whether it gives rise to a systemic immune response involving the airway mucosa at the site of the tubarian tube. Both mechanisms may be involved in the generation of allergic inflammation and swelling of the tubarian tube, ultimately leading to OME in predisposed patients.

10.6. Otitis media with effusion (OME)

During the last few decades, the etiologic relationship between rhinitis and otitis media, especially the role of allergy in OME, has been the subject of much controversy (15, 2131, 2132).

Otitis media with effusion is an inflammatory disease of the middle-ear mucosa. Otitis media with effusion remains a significant problem in the pediatric population. It is estimated that more than 80% of all children experience at least one episode of otitis media by the age of 3 and that 40% will have three or more future episodes (2133).

The nose and middle ears are situated in a system of contiguous organs. Both cavities are covered by respiratory mucosa and there is an anatomical continuity between these two cavities through the Eustachian tube. It is not fully understood whether inflammation, infection or obstruction in the nose influence or promote otitis media. There are several controversies with regard to the etiology and pathogenesis of OME, one of which being the relationship between allergy and OME. In view of the concept of global airway allergy, it can be expected that an allergic inflammatory response can also take place in the middle ear. Indeed, all cells and mediators that contribute to allergic inflammation are present in the middle-ear fluid of OME patients (2134, 2135). The middle-ear fluid of atopic patients with OME contains more eosinophils and IL-4 and IL-5 mRNA-positive cells as compared to nonatopic patients with OME (2122). This suggests a role of allergic inflammation in OME. Immunoglobulin E sensitization and respiratory allergy symptoms are independent risk factors for the development of OME (2136).

It is possible that children with atopic dermatitis present a higher prevalence of OME than nonatopic children (2137). In this large study, asthma and rhinitis were not predisposing factors for the development of OME. However, the number of OME episodes may be greater in atopic children than in nonatopic children (2138). It remains difficult to interpret epidemiologic data. The enhanced prevalence of allergy in OME patients reported by some authors (2139, 2140) may represent a true finding or may reflect a referral bias.

Many important questions still need to be answered:

- whether the presence of rhinitis predisposes an individual to the development of otitis;
- whether nasal dysfunction causes otitis to worsen;
- whether OME can be cured by treating the underlying nasal or sinus infection and
- whether the middle-ear mucosa can be targeted directly by allergens.

It is proposed that children with recurrent OME should be tested for allergy (2141, 2142).

10.7. Chronic cough

Cough is one of the most common symptoms for which patients seek medical attention (2143). The duration of cough and other symptoms and signs are the first steps to assess a patient presenting with cough.

Acute cough can be of viral origin (viral acute rhinosinusitis) but may be the first presentation of a more serious disease such as pneumonia, other respira-

tory infections, left ventricular failure, asthma or foreign body aspiration syndrome (2143).

Chronic cough is characterized by its duration of over 8 weeks (2143). It can be caused by a number of factors (1161, 2144–2146), including postinfectious cough (2147), allergic rhinitis (2148–2150), infection, rhinosinusitis (2151), asthma, COPD, gastro-esophageal reflux (2152), environmental stimuli such as tobacco smoke or occupational exposure (563, 564), bronchiectasis (2153), interstitial lung disease, congestive heart failure, drugs (ACE inhibitors, ß-blockers) (2154), thyroid disorders and psychogenic cough.

Postnasal drip secondary to a variety of rhinosinus conditions may be the most common cause of chronic cough (2155, 2156). Rhinitis is an independent risk factor for both recurrent cough and wheezing during childhood and adulthood (2148–2150). In patients with seasonal rhinitis, dry cough is common and often the predominant non-nasal symptom (1940).

In children, cough may be the only symptom of asthma (2157). Children who have a dry cough whilst exercising, laughing, playing with friends or in the middle of the night should be tested for asthma (2148, 2158).

Nasal treatment for allergic rhinitis with a steroid spray (2159) as well as oral H_1-antihistamines in adults (2160) have been reported to relieve the cough symptoms in allergic rhinitis patients. In children, oral H_1-antihistamines have not shown a convincing effect on chronic cough but more data are needed (2161).

Nonprescription treatment for cough in children under 6 years has been recently reviewed by a FDA panel and prohibited (2162).

10.8. Laryngitis

In patients with dysphonia, the presence of inhalant allergy is considered to be a hidden though common cause of vocal cord dysfunction (2163). However, the presence of vocal cord edema has not been proved to be induced by allergic inflammation. Furthermore, there is no study showing deleterious effects of allergen provocation on voice quality in atopic patients or beneficial effects of antiallergic therapy on laryngeal edema or voice quality. Inhaled steroids are often prescribed in patients with allergic asthma and may cause a reversible vocal cord dysfunction (2164).

Edema of the laryngeal mucosa, laryngeal erythema and candidiasis may all be found in a minority of patients treated with inhaled glucocorticosteroids (2165), but are not reported after the prolonged use of a nasal steroid spray.

10.9. Gastro esophageal reflux (GER)

Gastro esophageal reflux (GER) may masquerade as CRS (2166, 2167). Associations have been reported between GER and a variety of upper and lower respiratory tract conditions but not with allergic rhinitis (2168).

11. Rhinitis in children

Allergic rhinitis is the most prevalent chronic allergic disease in children (948). Although it is not life-threatening, it can have a significantly detrimental effect on a child's QOL, and it may exacerbate a number of common co-morbidities, including asthma and sinusitis (2169).

There are many different causes of rhinitis in children and approximately 50% are induced by allergy (2170). Allergic and nonallergic rhinitis are often difficult to differentiate based on symptoms.

As for asthma, preschool and older children should be considered separately.

11.1. The atopic march

The sequential development of allergic disease manifestations during early childhood is often referred to as the atopic march (2171). Various epidemiologic and birth-cohort studies have begun to elucidate the evolution of allergic disease manifestations and to identify populations at risk for disease (5, 2172–2174).

Atopic dermatitis is one of the most common skin disorders seen in infants and children. Usually, onset occurs during the first 6 months of life (2175). Epicutaneous sensitization has been thought to be responsible, with a subsequent migration of sensitized T-cells into the nose and airways, causing upper and lower airway disease (2175). Although atopy is associated to some degree with atopic dermatitis, its importance is not likely to be a simple cause-and-effect relationship, especially at a population level (2176). The prognosis of atopic dermatitis in infants is usually good, but the risk of developing asthma and allergic rhinitis is high (2177). However, the risk of subsequent childhood asthma may not be increased in children with early atopic dermatitis who are not also early wheezers, suggesting a co-manifestation of phenotypes in many patients rather than a progressive atopic march (2178). These associations may differ depending on the populations studied (2179).

A proportion of childhood eczema, rhinitis and asthma is nonatopic (2180). Not all children with an allergic sensitization will have atopic disease or develop symptoms after exposure to an allergen (1362, 2181).

Inhalant allergens may play an important role in the early development of asthma (2182). However, in preschool children, in contrast to older children, allergic rhinitis occurs at the same time or later than asthma (1049).

Food allergy is often the first sensitization to develop (885). Long-lasting sensitization to food precedes inhalant allergen sensitization (2183). Sensitization to indoor allergens occurs early in life (1843). Pollen sensitization

appears to occur later but, at 4 years of age, up to 11% of children may be sensitized (381). In general, at least two seasons of pollen allergen exposure are needed before allergic rhinitis clinically manifests (1049).

11.2. Epidemiology of rhinitis in preschool children

Despite the recognition that rhinitis affects an increasing proportion of preschool children, there is at present a paucity of epidemiologic data regarding its distribution, risk factors and natural history. Moreover, infectious rhinitis is extremely common and, like allergic rhinitis (2184), may be associated with episodic wheezing.

The prevalence of respiratory allergies in children from birth to 4 years is 6% while 4% are reported to have rhinitis (2185). Although the prevalence of rhinitis increases later in life (2186), the exact prevalence in preschool children is still a matter of discussion. By the age of 6, doctor-diagnosed allergic rhinitis may occur in more than 40% of children (721).

Risk factors for rhinitis in this age group are unclear and may include ETS and molds (251, 1900, 2187–2189). Birth cohort studies have shown that inhalant allergens are commonly involved (381, 1843, 2190, 2191).

11.3. Diagnosis

11.3.1. Preschool children. Allergic rhinitis and asthma in preschool children are difficult to diagnose, the symptoms often being confused with those of infectious rhinitis. However, symptoms that persist longer than 2 weeks should prompt a search for a cause other than infection.

In addition to sneezing, nasal itching, discharge and congestion, children with moderate/severe allergic rhinitis may develop noisy breathing, repeated throat clearing, snoring and a loss of olfaction and taste. They may also have facial manifestations of obstructed breathing, including a gaping mouth, chapped lips, hypertrophied gingival mucosa, a long face, dental malocclusions and allergic shiners. They also frequently have evidence of itching, e.g. an allergic salute or an allergic transverse nasal crease (2192). Their anterior cervical nodes may be enlarged. They may have malaise and disturbed nocturnal sleep with subsequent daytime fatigue. Co-morbidities associated with allergic rhinitis in children include asthma, atopic dermatitis/eczema, allergic conjunctivitis, chronic sinusitis and otitis media with residual or PER effusion.

Medical history is extremely important as it can reveal information regarding a family history of atopy and the progression of atopy in the child.

Skin prick tests can be performed and interpreted reliably early in life (1223). If positive, they yield evidence regarding atopy and sensitization to allergens. However, as for any other test, the results should be correlated with the child's symptoms and signs of allergic disease.

Although the presence of circulating IgE antibodies, as detected by Phadiatop Pediatric, could predict the development of atopic diseases during childhood, the usefulness of the test in preschool children was limited by its low sensitivity (22–47%; 2193). The recently developed Phadiatop-infant may be more sensitive and specific (2194, 2195). Positive tests to food allergens in infancy predict a later development of sensitization to inhaled allergens (2196). The combination of Phadiatop and fx5 (mixed food allergy muli-IgE test) has been reported to be a reliable way of identifying the likelihood of allergic diseases in young children (1363). However, food allergens do not trigger allergic rhinitis as such, although they may trigger nasal symptoms during full-blown severe acute allergic reactions (anaphylaxis) to food.

Elevated levels of total-serum IgE are not a good predictor of atopy since levels vary widely with age (2197). Elevated total IgE levels are more likely to correlate with the presence of atopic dermatitis than with allergic rhinitis.

The differential diagnosis of allergic rhinitis in preschool children includes infectious rhinitis (usually viral), foreign body, anatomical variations including unilateral choanal atresia, benign tumors including dermoid cysts and meningoencephalocele, cystic fibrosis and related diseases (2198–2200), mucociliary dyskinesia (1340, 2201) or nasal obstruction induced by adenoid hypertrophy (15).

11.3.2. Older children. The differential diagnosis of allergic rhinitis in older children also includes trauma (septal haematoma, fractured nasal bones and synechiae), cerebrospinal fluid rhinorrhoea, nasal glioma and *rhinitis medicamentosa* involving the overuse of topical decongestants. Nasal polyps are uncommon in children, and if they are observed, the diagnosis of cystic fibrosis must be considered.

11.4. Treatment

11.4.1. Pharmacologic Treatment. Allergic rhinitis and asthma are common in preschool and school children and are often associated with each other (2202). Children on asthma-controller therapy are frequent users of rhinitis medications (2203). It is therefore important to carefully assess the side effects of treatments, especially in children with both rhinitis and asthma (2204).

The principles of treatment are the same in children as in adults, but special care has to be taken to avoid the side effects which are unique to this age group (59, 2170, 2205). Dosages have to be adapted and certain special considerations have to be followed. Caution is necessary because of the young age of the patient. Among the most important aspects to consider are the cognitive functions of preschool and school children in relation to the general malaise caused by rhinitis and in relation to the antihistamine treatment.

Many medications currently prescribed for children with allergic rhinitis lack full pediatric approval. Doctors should bear in mind that developmental changes in infancy and childhood can profoundly affect medication absorption, distribution, metabolism and excretion, and that this, in turn, can affect optimal dosing, efficacy and safety. Of particular concern are any adverse effects involving impairment of growth or cognitive development. Pediatric doses of some medications used in allergic rhinitis treatment (e.g. certain older H_1-antihistamines and intranasal glucocorticosteroids) are based on extrapolations from clinical pharmacology data obtained in adults and teenagers rather than on data obtained directly from studies in children, especially preschool children and infants. Few drug treatments have been tested in infants and preschool children (2206–2209). In the future, it is hoped that package inserts for the medications used in allergic rhinitis treatment will include fewer disclaimers that 'safety and efficacy are not established in infants and young children'.

Oral glucocorticosteroids and depot-preparations should be avoided in the treatment of rhinitis in young children. Intranasal glucocorticosteroids are the most effective treatment of allergic rhinoconjunctivitis but the parental fear of systemic side effects, which are actually uncommon, should always be considered. Modern intranasal glucocorticosteroids are much less absorbed (bioavailability $<30\%$) and the minimal dose needed to control symptoms should be used. Intranasal glucocorticosteroids with high bioavailability such as betamethasone should not be used in children (2210). One special concern is the effect upon growth and growth velocity. In children, the rate of growth was slightly reduced in those regularly treated with intranasal beclomethasone for over 1 year (1575). However, no growth retardation has been observed in 1-year follow-up studies of children treated with fluticasone propionate, mometasone furoate or triamcinolone acetonide (1578, 1579, 2211–2213). Moreover, a pharmacokinetic/pharmacodynamic model of the relationship between systemic corticosteroid exposure and growth velocity has been proposed and may be useful for the development of future local glucocorticosteroids. On the other hand, oral and depot glucocorticosteroid preparations have a clear effect on growth and growth velocity (2214).

Intranasal glucocorticosteroids do not appear to have an effect on the hypothalamic-pituitary-adrenal-axis in children (1570, 2215, 2216). The concurrent use of intranasal and orally-inhaled fluticasone propionate does not affect the hypothalamic-pituitary-adrenal-axis function (1568).

Mometasone furoate is available for children of 2 years and over (2217–2219). Fluticasone propionate is approved for children aged 4 years and older (2213, 2220–2222), and other intranasal glucocorticosteroids may be used in those over the age of 5 years (1518, 2223, 2224).

The use of H_1-antihistamines is important for the treatment of allergic rhinitis in children, as many young children particularly prefer an oral medication to an intranasal medication. First-generation oral H_1-antihistamines have central nervous system side effects, including sedation and fatigue (116, 2225). Paradoxical hyperactivity, insomnia and irritability may also occur in infants and very young children. Seasonal allergic rhinitis *per se* may affect learning ability and concentration. Treatment with first-generation H_1-antihistamines often has a further reducing effect upon cognitive function (2226). However, use of the newer H_1-antihistamines counteracts the feeling of malaise caused by allergic rhinitis and may improve learning ability in allergic rhinitis. Pharmacokinetic studies of the second-generation H_1-antihistamines have been performed on children, but few studies have been carried out on infants (116, 2227–2229). Interactions with the cytochrome P450 may reduce the metabolism of the H_1-antihistamines metabolized in the liver. Macrolide antibiotics, commonly used in children, may have this effect. Cetirizine, fexofenadine and levocetirizine are not metabolized to any extent. Moreover, while many second-generation H_1-antihistamines are effective and safe in the treatment of allergic rhinitis in children, only cetirizine, levocetirizine and loratadine have been studied for long-term efficacy and safety in children (2230–2232).

The use of intranasal H_1-antihistamines like levocabastine and azelastine has the benefits of rapid onset of action and few adverse effects. However, although there is a beneficial effect upon symptoms in the organ to which they are administered, they usually have little effect elsewhere. These drugs are useful in children with symptoms limited to the nose or the eyes (1408, 2233, 2234).

In some countries, montelukast is approved for the treatment of allergic rhinitis in children.

The pharmacokinetics of oral decongestants appear to differ in children and adults and more studies are needed (1611). These medications may also contribute to hyperactivity and insomnia in children.

Disodium cromoglycate has been one of the common drugs used for allergic rhinoconjunctivitis in children but it is less effective than intranasal glucocorticosteroids or H_1-antihistamines (2233, 2235, 2236). It is important to note that in children, these drugs are free from side effects. However, a dosage of four to six times a day is required for cromoglycate, and compliance with treatment is often difficult. Nedocromil sodium has been studied in children (2237) but has gained less acceptance.

Nasal saline drops or spray can help to clear the nose before eating or sleeping (2238).

Pharmacologic management must be individualized and polypharmacy must be avoided (2148, 2239).

11.4.2. Nonpharmacological treatment. Nonpharmacologic treatment of allergic rhinitis in children involves educating the family and the child about the recurrent or PER nature of the disease, and avoiding allergen triggers and respiratory tract irritants, the most important of which is tobacco smoke.

Allergen-specific subcutaneous immunotherapy is not usually recommended before the age of 5 y due to safety concerns as well as difficulties in performing serial injections of allergens over months or years (2240). There are some preliminary studies on SLIT in preschool children (1721, 2241). It has been found to be safe but its efficacy needs to be tested further. Moreover, SLIT in young children with allergic rhinitis may possibly prevent a later development of asthma.

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